

Postural Stability and Fall Risk in Adult Familial Mediterranean Fever Patients

Ailevi Akdeniz Ateşi Olan Erişkin Hastalarda Postural Stabilite ve Düşme Riski

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ABSTRACT

Objective: In this study, our purpose was to determine the postural stability and fall risk by an objective computerized technique in patients with Familial Mediterranean Fever (FMF), together with their relevant potential risk factors for falls.

Materials and Methods: 45 patients diagnosed with FMF (mean age 31±10 years; range 17 to 53 years) and 40 healthy controls (mean age 31±9 years; range 18 to 50 years) were included in the study. We used the Falls Efficacy Scale (FES-I) for assessment of fall efficacy. The disease severity score was assessed. Stability Index (SI), Weight Distribution Index (WDI), and fall risk analysis were performed by the computerized posturography device.

Results: Significant differences were found between groups regarding SI and WDI values ($p<0.05$). The risk of falling ($p=0.003$) and the history of falls in the last year in the patient group ($p=0.031$) were found to be higher. However, except for female gender and FES-I, no significant relationships were found between fall risk and disease-related factors such as age, body mass index, severity, and duration of the disease, the last 1-year fall history ($r<0.3$, $p>0.05$). Moreover, while significant positive correlations were determined between all parameters of SI and fall risk ($r>0.3$, $p<0.001$), no relationship was found between WDI and fall risk ($r<0.3$, $p>0.05$) except close eyes-head extended (HB-WDI; $r=0.003$, $p<0.001$).

Conclusion: Postural stability was impaired, and fall risk increased in FMF. This result might result from FMF disease or many other factors being capable of affecting the balance.

Key Words: Familial Mediterranean Fever, postural stability, fall risk

ÖZET

Amaç: Bu çalışmada, Ailevi Akdeniz Ateşi (AAA) olan erişkin hastalarda düşme için olası risk faktörleri ile birlikte objektif bilgisayarlı bir teknik kullanılarak postural stabilite ve düşme riskinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya AAA hastalığı tanısı konulan 45 hasta (ortalama yaş: 31±10 yıl, yaş aralığı: 17-53 yıl) ile yaş ve cinsiyetleri benzer olan 40 sağlıklı kontrol (ortalama yaş:31±9 yıl, yaş aralığı: 18-50 yıl) dâhil edildi. Düşme etkinliğinin değerlendirilmesi için uluslararası düşme etkinliği ölçeği (U-DEÖ) kullanıldı. Hastalık şiddeti skoru değerlendirildi. Bilgisayarlı posturografi cihazı ile; postural stabilite için stabilite indeksi (Sİ) ile ağırlık dağılım indeksi (ADİ) ve düşme riski analizi yapıldı.

Bulgular: Bilgisayarlı sistem kullanılarak ölçülen Sİ ve ADİ değerlerinde gruplar arasında anlamlı fark bulundu ($p<0.05$). Hasta grupta düşme riski ($p=0.003$) ve son bir yıldaki düşme öyküsünün ($p=0.031$) daha yüksek olduğu tespit edildi. Ancak kadın cinsiyet ve U-DEÖ hariç yaş, vücut kitle indeksi, hastalık süresi, hastalık şiddeti, son 1 yıl içindeki düşme öyküsü gibi ilişkili faktörler ile düşme riski arasında herhangi bir ilişki bulunamadı ($r<0.3$ ve $p>0.05$). Ayrıca Sİ'nin tüm parametrelerinde düşme riski ile arasında anlamlı pozitif bir ilişki tespit edilirken ($r>0.3$ ve $p<0.001$), ADİ ile düşme riski arasında gözler kapalı ve baş ekstansiyonda iken (HB-ADİ; $r=0.003$, $p<0.001$) hariç bir ilişki bulunamadı ($r<0.3$ ve $p>0.05$).

Sonuç: AAA hastalığında postural stabilitenin bozulduğu ve düşme riskinin arttığı anlaşıldı. Bu sonuç AAA hastalığından veya dengeyi etkileyebilen diğer birçok faktörden kaynaklanmış olabilir.

Anahtar Kelimeler: Ailevi Akdeniz Ateşi, postural stabilite, düşme riski

Introduction

Familial Mediterranean fever (FMF) is a multisystemic disorder characterized by recurrent painful episodes affecting the abdomen, chest, and

joints. It is frequently accompanied by fever, and rarely by skin rashes. Patients are asymptomatic and completely healthy between FMF episodes. Chronic, long-lasting symptoms such as nephropathic amyloidosis, chronic arthritis, and

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protracted myalgia may be manifest in this disorder (1).

Disorders in postural stability may lead to balance problems and increase the fall risk in rheumatic diseases (2-5). Falling may have various consequences such as loss of confidence, injuries, and even death (6). Even though falls are considerably common in rheumatic diseases and frequently have serious results, they are still not investigated and have not been given importance enough in the population. Moreover, most of the previous studies on the fall risk in rheumatic diseases were conducted in diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and systemic lupus erythematosus (SLE) (5).

To our knowledge, no study has been conducted on postural stability and fall risk in adult FMF patients yet. Determining the status of postural stability, the fall risk, and the related risk factors may lead to awareness and prevention of falls and may contribute to the management of such patients. In this study, we aimed to determine the postural stability and fall risk in FMF patients with an objective computerized technique and to evaluate the potentially related risk factors for falls in these patients.

Materials and Methods

This cross-sectional study was conducted between November 2018 and March 2019 by the Department of Physical Medicine and Rehabilitation at Atatürk University Medical Faculty. A total of 45 patients (mean age 31 ± 10 years; range 17 to 53 years) who were diagnosed with FMF according to the criteria determined by Livneh et al. (7) and 40 healthy controls (mean age 31 ± 9 years; range 18 to 50 years) with similar age and gender were included in the study. Patients who could not tolerate and cooperate during the posturographic assessment, who had a history of orthopedic or spinal surgery, a muscular disorder, neurological disorder, limitation of movement, motor insufficiency, inflammatory arthritis, degenerative osteoarthritis, vertigo, diabetes mellitus, audiological and ophthalmological disorders were excluded from the study. The study protocol was approved by the Medical Faculty of Atatürk University Ethics Committee (29.11.2018/7;2). Written informed consent was received from each subject. The study was conducted in conformity with the precepts of the Declaration of Helsinki.

The gender, age, body mass index (BMI), duration of the disease, duration, and dose of colchicine use, the last 1-year history of falls, and FES-I value were recorded. The patients were receiving colchicine with an oral dose of 0.5-2 mg daily. No drug other than colchicine that could lead to balance loss was being used by the participants. In addition, the severity of the disease was scored in the patients. The FMF disease severity scores were calculated based on the age at disease onset (>31 , 21-31, 11-20, 6-10, <6 years; 0,1,2,3,4 points, respectively) number of attacks per month (<1 , 1-2, >2 ; 1,2,3 points, respectively), arthritis status (acute and protracted; 2 and 3 points, respectively), amyloidosis status (presence 3 points), colchicine dose (1,1.5,2 and >2 mg; 1,2,3 and 4 points, respectively) and the presence or absence of erysipelas-like erythema at the time of admission (presence 2 points). Scores of 3-5, 6-8, and ≥ 9 were considered to reflect mild, moderate, and severe disease, respectively (8).

For the evaluation of fall efficacy in patients with FMF, we used the Falls Efficacy Scale International (FES-I); FES-I is a self-reported questionnaire that assesses the level of concern about falls during daily activities. The reliability and validity of the Turkish version of FES-I were performed by Ulus et al. (9).

Postural stability and fall risk analysis of patients with FMF and the controls were performed by using the Tetrax Interactive Balance System (Sunlight Medical Ltd., Tel Aviv, Israel) with the same technique directed by the user's guide of the device (10-11). In the Tetrax system, the posturographic assessment consists of two configurations based on detailed balance and fall index evaluations. In detailed balance assessment, the stability index (SI), based on evaluation of shifting of the center of gravity, involves the Fourier transformations, which consist of four independent wave signals and divided into eight frequency bands, the measurement of weight distribution on four platforms (WDI), and the synchronization measurements reflecting the efficacy and quality of the coordination movements between the heel and fingers of each foot. The analysis of postural performance is realized by comparing the above-mentioned four measurements used for detailed balance assessment in eight different positions. These eight different positions are eyes open and closed – head neutral (NO-NC), eyes open and closed – sponge pad under the feet – head neutral (PO, PC), eyes shut – head rotated to the right and left (HR, HL), and eyes closed – head fully extended

and flexed (HB, HF). With the help of these postural measurements, a falling index derived from the Tetrax balance parameters was developed to produce a score that will express the patient's risk of falling based on the specific balance factors that affect falling. Fall risk is a numeric value ranging from 0 to 100, with three risk groups, indicating low (0 to 35), moderate (36 to 57), or high (58 to 100) risk of fall (11-12).

Statistical Analysis: In our study, a power analysis was performed for fall risk with 95% power and 95% confidence interval. The mean values for fall risk were 45.7 ± 27.13 for the patient group and 29.25 ± 18.6 for the control group. Statistical analysis was performed by the statistical analysis software SPSS version 20, IBM. Data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. The Shapiro Wilk test was used for the conformity of the continuous variables with the normal distribution. When conformity with normal distribution was present in the comparisons between the two independent groups, the Independent Samples T-test was used, and when normal distribution was not provided, the Mann Whitney U test was used. The comparisons between the categorical variables were performed by the Chi-square and Fisher's Exact tests. When conformity with normal distribution was present regarding the relationship of two quantitative variables, Pearson's test was used, and when absent, the Spearman correlation test was used. The level of statistical significance was considered as $p < 0.05$.

Results

The demographic data of the patients and the healthy individuals were shown as a summary in Table I. No statistically significant differences were found between the patients and healthy controls regarding age, gender, and BMI ($p > 0.05$). The mean duration of the disease was 8 ± 5 years, and the mean duration of colchicine use was 6 ± 5 years in the patient group. Five patients were using colchicine with a dose of 0.5 mg/day, 22 patients 1 mg/day, 15 patients 1.5 mg/day, and two patients with a dose of 2 mg/day orally, whereas one patient was not using colchicine.

There was a significant difference between the groups regarding the fall history; five patients with FMF had a total count of 11 falls in the last year ($p = 0.031$). No significant difference was found to be present between the groups regarding the FES-I score ($p > 0.05$).

Regarding the parameters investigated for disease severity, the score for the age of disease onset was 0 point in 12, 1 point in 13, 2 points in 8, 3 points in 11 individuals whereas one individual had a score of 4; the score for the number of febrile episodes per month was 1 point in 29, 2 points in 14, and 3 points in three individuals; the arthritis score was 0 points in 37, and 2 points in seven individuals whereas one individual had a score of 3 points; the score for the presence of erysipelas-like erythema was 0 point in 39, and 2 points in six individuals; the score for the presence of amyloidosis was 0 point in 42, and 3 points in three individuals. The score of colchicine dose was determined as 0 points in one individual, whereas it was 1 point in 27, 2 points in 14, and 3 points in two individuals. The mean value of the total score for disease severity was determined as 5 ± 2 (Table 1).

Regarding the comparison of postural stability between the groups, the general SI scores were shown in eight positions. Significant differences were found to be present between the groups regarding the PC-SI ($p = 0.001$), HL-SI ($p = 0.042$), and HF-SI values ($p = 0.045$) (Table 1). Moreover, significant positive correlations were determined between all parameters of SI and the fall risk ($r > 0.3$ and $p < 0.001$). Regarding the comparison of postural stability between the groups, the WDI scores were shown in eight positions (Table 1). Significant differences were found to be present between the groups regarding the PO-WDI ($p = 0.005$) and PC-WDI scores ($p = 0.011$). However, except for HB-WDI ($r = 0.003$, $p < 0.001$), no other correlation was present between WDI and the fall risk ($r < 0.3$ and $p > 0.05$) (Table 2). A significant difference was found between the groups regarding the fall risk analysis performed through a computerized system ($p = 0.003$) (Table 1).

No significant relationships were found between BMI, duration of the disease, duration and dose of colchicine use, disease severity, the last 1-year fall history values, and the fall risk ($r < 0.3$ and $p > 0.05$). A significant relationship was found to be present between fall risk with the female gender and FES-I values ($p = 0.016$) (Table 2). In addition, low-level fall risk was established in the control group, and a significant relation was ascertained between the fall risk and SI ($p < 0.001$) (Table 2).

Discussion

The study investigated postural stability, fall risk, and the possible related factors and found that postural stability was impaired, and the fall risk

increased. In these patients, a significant relationship only with female gender and FES-I values was established regarding the factors that we consider as might be associated with increased fall risk. This result might result from FMF disease or many other factors being capable of affecting the balance.

Posturography is an objective and digital method used for the evaluation of postural stability and balance (13). It evaluates the current postural state by measuring postural sways (14-15). Postural stability is defined as the capability of the body to

Table 1. Comparisons of factors between familial Mediterranean fever patients and controls

	Patients (n=45)					Controls (n=40)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	p
Sex (M/F)	21/24					18/22					0.878
Age (year)			31±10					31±9			0.454
BMI (kg/m ²)			24.1±4.3					25.5±3.4			0.123
Disease duration (years)			8±5					-			
Disease severity score			5±2					-			
Falls history		11					0				0.031*
FES-I			21±6					21±6			0.887
SI values											
NO-SI				15.3	9.7-58				14.5	10-78.7	0.758
NC-SI				20.4	10.1-46.1				19.5	13.7-31.7	0.487
PO-SI				16.7	10.9-34.1				16.4	12.3-38.1	0.238
PC-SI				28.3	16.2-53.8				24.3	16.2-40	0.001**
HR-SI				18.9	10.6-37.9				19.4	12.1-37.4	0.802
HL-SI				22.2	9.1-78.2				20	13.6-28.1	0.042*
HB-SI				24.2	11.5-61.1				21	14.4-40.1	0.08
HF-SI				22	10.7-64.6				19	11.1-32	0.045*
WDI values											
NO-WDI				5.4	1-15.7				5.6	1.1-13.7	0.761
NC-WDI				5.7	2.1-14.7				5	1.7-15.6	0.386
PO-WDI				7.7	1.8-20				5.8	1.5-11.8	0.005**
PC-WDI				7.6	2.2-14.2				6.1	0.7-10.6	0.011*
HR-WDI				4.9	1-14.2				4.6	1.8-18.7	0.951
HL-WDI				5.4	1.5-13.3				4.8	1.1-13.6	0.745
HB-WDI				6	1.3-14				5.8	0.8-15.9	0.867
HF-WDI				4.9	1.2-11.5				5.2	0.9-16.7	0.933
Fall risk assessment (0-100)				40	4-100				26	4-88	0.003**
Fall risk category											
Low		19					30				
Moderate		15					5				
High		11					5				

SD: Standard deviation; Min: Minimum; Max: Maximum; M: Male, F: Female, BMI: Body mass index; FES-I: Falls Efficacy Scale International, SI: Stability Index, WDI: Weight Distribution Index, NO: open eyes- head neutral, NC: closed eyes- head neutral, PO: open eyes-sponge pad under the feet, PC: closed eyes-sponge pad under the feet, HR: closed eyes – head rotated to the right, HL: closed eyes – head rotated to the left, HB: closed eyes – head fully extended, HF: closed eyes – head fully flexed, *. P <0.05 was considered as statistically significant between patient and control groups, **. p<0.01 was considered statistically significant between patient and control groups

maintain its balance. This capability is an important index of physical functions and strongly related to fall risk (13). Moreover, postural stability problems encountered in rheumatic diseases may lead to balance disorders and increase the fall risk (2-5).

It was suggested that having various rheumatic disorders is the second strongest independent risk factor for serious falls, leading such patients to be under even more increased fall risk (6). Among the risk factors causing falls are age, gender, history, and fear of falls, physical condition, cognitive functions, inadequate physical activity, and environment.

FMF is a chronic disease characterized by abdominal pain, arthritis, chest pain, and synovitis. Therefore, encountering synovitis-related pain may lead to a reduction of balance control in FMF patients. For this reason, since our patients had encountered neither pain nor attack during the study, we think that pain did not play any role as the cause of a balance disorder (16).

In our study, impaired postural stability and increased fall risk were found in FMF patients. The number of falls in the last 1-year history was significantly higher in the patient group. While significant associations of fall risk values with female gender and FES-I values were found, no relationships of them were determined with related factors such as age, BMI, disease duration and severity, the last 1-year fall history. In addition, a positive correlation was determined between SI and the fall risk.

To our knowledge, no study investigating the effects of FMF on postural stability and fall risk in adults has been presented in the literature. Yilmaz et al., in their study conducted in pediatric FMF patients, reported that postural stability was reduced in the patient group compared to controls, and additionally that the postural stability index values were related to colchicine dose, but not to disease severity. In the same study, they also found a significant difference between groups in girls. However, in that study, no fall risk-related analysis was performed (16). Like the study mentioned above, a reduction in postural stability was determined in our study. However, no relationships were found to be present between the duration and dose of colchicine use and postural stability and fall risk. This might have been due to a milder clinical course of colchicine-related neuromyopathy in adults compared to pediatric patients. Moreover, since the muscle power and balance ability are increased in adults compared to children, colchicine-related neuromyopathy might

have been compensated. In our study, like the study mentioned above, significant relationships were found between female gender, SI, and fall risk. In addition, a significant difference was determined between the groups regarding fall history. A total of five cases in the patient group, consisting of three females and two males, had a positive fall history. While the female cases had fallen nine times, the male cases had fallen only twice. Conducted studies have also shown that female patients had an increased incidence of falls and that gender was a risk factor (17).

Aydoğ et al. (2). reported that postural stability was impaired in patients with rheumatoid arthritis (RA), whereas the activity and duration of the disease had no effect on postural stability. They reported that balance was affected by the functional status rather than the disease activity, and that age and BMI were the most significant factors for postural stability in both the patient and control groups (2). In our study, no significant association was found between age, BMI, and postural stability. This result might have been due to the increasing destructive effect of RA on the musculoskeletal system with increasing age, the possibility of balance loss being related to other associated factors related to advanced age, the number of their patients being more when compared to ours, and individual factors such as muscle strength.

Melikoğlu et al. (5), in their study, determined that the fall risk increased in SLE patients; however, they provided no data related to postural stability values. There was a significant difference in FES-I values between the groups. In addition, in that study, among numerous evaluated parameters, only FES-I was found to have a significant relationship with the fall risk (5). The higher fall risk determined in their SLE patients compared to the moderate fall risk that we found in our FMF patients might have been related to the fact that their SLE patients were selected only from female patients, the more advanced age of their patients, and the possibility of the presence of other comorbidities in their patients. In addition, there was a significant positive relationship between FES-I and risk of falling similar to the study of Melikoglu et al.

In another study investigating postural stability and fall risk in patients with fibromyalgia, increased postural instability, and fall incidence was reported. In the same study, it was also reported that poor postural performance and increased fall risk in fibromyalgia patients were associated with the fatigue level and the last-24-hour sleep quality (18). The parameters such as fatigue and the last-24-hour sleep quality, which are clinical features specific to

Table 2. The correlation between demographic, clinical, stability index and weight distribution index values with fall risk

	FMF patients (fall risk)		Healthy controls (fall risk)	
	r	p	r	p
Age (year)	-.136	0.213	-.133	0.414
BMI (kg/m ²)	-.080	0.465	-.066	0.686
Disease duration (years)	.184	0.225	-	-
Disease severity score	.156	0.306	-	-
Falls history	.019	0.901	-	-
FES-I median	.358	0.016*	.353	0.026*
SI values				
NO-SI	.522	.000**	.440	.004*
NC-SI	.505	.000**	.540	.000**
PO-SI	.502	.000**	.626	.000**
PC-SI	.585	.000**	.585	.000**
HR-SI	.533	.000**	.606	.000**
HL-SI	.540	.000**	.500	.001**
HB-SI	.544	.000**	.581	.000**
HF-SI	.662	.000**	.692	.000**
WDI values				
NO-WDI	.192	.079	.092	.571
NC-WDI	.259	.017*	.110	.501
PO-WDI	.182	.096	.055	.735
PC-WDI	.174	.111	-.099	.545
HR-WDI	.218	.045*	.066	.687
HL-WDI	.242	.026*	.061	.709
HB-WDI	.319	.003*	.174	.283
HF-WDI	.248	.022*	.104	.522

SD: Standard deviation; Min: Minimum; Max: Maximum; M: Male, F: Female, BMI: Body mass index; FES-I: Falls Efficacy Scale International, SI: Stability Index, WDI: Weight Distribution Index, NO: open eyes- head neutral, NC: closed eyes- head neutral, PO: open eyes-sponge pad under the feet, PC: closed eyes-sponge pad under the feet, HR: closed eyes – head rotated to the right, HL: closed eyes – head rotated to the left, HB: closed eyes – head fully extended, HF: closed eyes – head fully flexed, *. Correlation is significant at the 0.05 level, **. Correlation is significant at the 0.01 level

fibromyalgia syndrome were not investigated in our study.

It was reported in patients with ankylosing spondylitis (AS) that postural stability was reduced in both the early and the late stages, and that this result might have been associated with increased kyphosis observed during the clinical course of the disease (19). However, there are also studies reporting that no impairment in postural stability occurs in AS patients (20). Giacomini et al. stated in their study that a subtle neurophysiological dysfunction was present in postural stability in patients with systemic sclerosis, and further somatosensory neurological function tests would be required for interpretation of this finding (21).

The stability index, measured by an objective computerized system used in our study and which is among the postural stability parameters for

assessment of general balance status, is a required mathematical and numerical result expressing the amount of postural sway. The stability index is interpreted as the numerical expression of the alterations seen in the balance parameters of clinically undetectable postural disorders, together with their controls and compensations. A higher value indicates a higher imbalance level of the individual, and a lower value indicates a higher balance status and stability. By our second parameter, weight distribution index (WDI), non-symmetrical distributions between the right and left feet, heels, finger regions, and their cross-interactions are observed. A high WDI on a 4-foot platform indicates the mismatch of weight percentage of each foot, and it is the indicator of pathology. A value close to zero is the indicator of maximum postural stability and frequently produced

by compensatory balancing mechanisms. In our study, the higher values of the stability index, PC-ST, HL-ST, and HF-ST in the FMF patients suggested that the severity of balance impairment was more. Thus, a significant positive correlation was determined between the fall risk and all parameters of SI, which showed the general balance status. The higher weight distribution index, PO-WDI, and PC-WDI values found in the study might be the indicator of the insufficiency of other compensatory mechanisms for postural stability and maximum good posture. However, even though no significant difference was present between the groups regarding the HB-WDI value, a positive correlation was found between HB-WDI and the fall risk. This position is particularly affected by the disorders of the central and peripheral vestibular systems. Therefore, this situation might be related to an unidentified pathology.

Even though fall has been accepted to be observed frequently in patients with rheumatic disorders, studies on the fall risk in this population are not enough. The wide range of fall incidence (from 10% to 50%) has been reported due to inconsistencies in obtaining fall-related data and the limited amount of information provided in the studies methodologically conducted for the assessment of the fall risk in various rheumatic diseases, particularly RA (9). In our study, similar to the studies on the other rheumatic diseases, the fall risk in FMF patients was found to be categorically at a moderate level (40%). Due to the low-level fall risk (26%) established in the control group, a positive correlation was determined between the low-level fall risk and its SI values. But, since it is not required to take any precautions in advance for the low-level fall risk, it is not clinically significant.

An increase was established in acute phase reactants in FMF except for the attack stages, which indicates a continuous subclinical inflammation. The researches on the subject linked the continuous inflammation with the increased serum amyloid A. This subclinical inflammation in FMF might result in impulse disorder coming from visual, somatosensory, or proprioceptor sensory source. Consequently, loss of balance and fall risk might increase. In addition, the muscle strength, the fatigue level during measurement, and the last 24-hour sleep quality of the participants might have effects on postural stability, and therefore the risk of falling. Because of such a moderate risk of falling, FMF patients should exercise regularly, and be careful while walking and running. In addition, they should take the necessary precautions to prevent slipping while being in contact with slippery surfaces

or walking. Moreover, our study might raise awareness on chronic inflammatory processes in individuals with rheumatic disorders, fractures that might occur due to osteoporosis, which can develop particularly in women and advanced age, together with the prevention of their complications.

A limitation of this study is its small sample size. Thus, a larger sample size, including several involvements seen in FMF, may provide more significant results.

In our study, it was determined that the postural stability was impaired, and the risk of falling was increased in FMF disease. This result might result from FMF disease or many other factors being capable of affecting the balance. Future studies investigating the possible coexisting balance problems in FMF may contribute to the management of the disease.

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