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ORIGINAL ARTICLE

Evaluation of peripheral nerve involvements in patients with familial Mediterranean fever

Atak Karabacak[1], Rahşan İnan[1], Nesrin Şen[2]

[1]Department of Neurology, University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[2]Department of Rheumatology, University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

ABSTRACT

Objectives: The aim of this study was to evaluate possible peripheral and autonomic nerve involvement in familial Mediterranean fever (FMF) patients with nerve conduction studies, sympathetic skin response (SSR) and RR interval variability (RRIV).

Patients and methods: The comparative case series was conducted with 76 participants between November 2017 and December 2018. Forty-six FMF patients, [12 with amyloidosis (5 males, 7 females; mean age: 44.7±13.9 years) and 34 without amyloidosis (14 males, 20 females; mean age: 35.9±8.7 years)], and 30 healthy volunteers (11 males, 19 females; mean age: 38.4±10 years) were included in this study. Nerve conduction parameters, SSR latency and amplitude from palmar and plantar responses, and RRIV at rest and deep breathing were studied in all the subjects. Neuropathic symptoms of the patient group were evaluated using the survey of autonomic symptoms scale and the neuropathy disability score.

Results: Nerve conduction studies of the patient group revealed polyneuropathy in seven (15.21%) patients and carpal tunnel syndrome in six (13.04%) patients. The mean amplitudes of SSR measured from the soles were significantly lower than the control group (p=0.041). The mean values of RRIV during rest and hyperventilation were lower in the patient group compared to the control group, but no statistically significant difference was found (p=0.484, p=0.341).

Conclusion: We detected that the prevalence of carpal tunnel syndrome in our patient population (13.04%) was higher than in the general population. Most of the changes in the range of parameters of SSR and RRIV determined in the patient group did not reach statistical significance, suggesting subclinical dysautonomia in FMF patients.

Keywords: Autonomic nervous system, familial Mediterranean fever, peripheral nervous system, sympathetic skin response.

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease in the world. It is distinguished by self-limiting fever and polyserositis attacks.[1,2] The most severe complication of the disease is the accumulation of amyloid in the tissues. The type of amyloid accumulated in FMF patients is secondary (AA) amyloidosis. Although peripheral neuropathy is a common complication in familial and primary amyloidosis, it is not an expected complication in AA-type amyloidosis. Nevertheless, there are few case reports of upper limb mononeuropathy and autonomic neuropathy in the literature that are thought to develop due to AA amyloidosis.[3-6] A study examining the parameters of heart rate variability in severe and complicated FMF patients with amyloidosis revealed a significant difference compared to healthy controls.[7]

In this study, we aimed to investigate the frequency of peripheral nerve and autonomic nerve involvement in adult FMF patients. For this purpose, electrophysiological peripheral nerve conduction examinations and autonomic function tests were studied in patients with and without

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Correspondence: Nesrin Şen, MD. SBÜ, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Romatoloji Kliniği, 34865 Kartal, İstanbul, Türkiye.
E-mail: sennes77@yahoo.com

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amyloidosis and in healthy volunteers, and the results obtained were compared. The presence of neuropathic and autonomic involvements in the patient group were evaluated using the neuropathy disability score (NDS) and the survey of autonomic symptoms scale (SAS), respectively.[8,9]

PATIENTS AND METHODS

The comparative case series study was carried out with 76 participants (46 females, 30 males; mean age: 38.3±10.9 years; range, 18 to 69 years) at the University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital between November 2017 and December 2018. Inclusion criteria for the subjects were being over 18 years of age and having a clinical, genetic, or biopsy-confirmed FMF diagnosis. The control group included individuals who matched the three patient groups in terms of age and sex, without a history of systemic disease, drug usage, and no signs of polyneuropathy during clinical examination and nerve conduction studies. A total of 46 FMF patients [12 AA amyloidosis positive (5 males, 7 females; mean age: 44.7±13.9 years) and 34 amyloidosis negative (14 males, 20 females; mean age: 35.9±8.7 years)] and 30 healthy volunteers (11 males, 19 females; mean age: 38.4±10 years) from the rheumatology and nephrology outpatient clinics of our hospital were included in the study. All amyloidosis-positive patients were diagnosed according to renal or rectal biopsy. Amyloidosis-negative patients were distinguished by the absence of proteinuria in routine urine analysis.

Routine peripheral nerve conduction studies in the upper and lower extremities and sympathetic skin response (SSR) and RR interval variability (RRIV) were studied in all participants. All participants were asked not to smoke, drink caffeinated beverages, or take other stimulants 3 h prior to the electrophysiological examinations. Room temperature was maintained at 21-24°C.

Median, ulnar, radial sensory, and motor nerve conduction studies and median F responses were studied in the upper extremity. In the lower extremity, tibial and peroneal motor responses, sural and superficial peroneal sensory conduction studies, and tibial F responses were examined. Nerve conduction studies on the opposite extremity were additionally performed in case of any abnormality.

Palmar and plantar sympathetic skin responses were recorded on the right upper and lower extremities. After skin cleaning, the active electrode was placed in the palm, the reference electrode was placed on the back of the hand, and the ground electrode was placed on the wrist. In the lower extremity, the active electrode was placed on the sole of the foot, the reference electrode was placed on the back of the foot, and the ground electrode on the ankle. The stimulating electrodes were placed over the contralateral median and tibial nerves. The frequency filter settings of the device were set at 0.5-3 kHz and the sweep speed at 0.5 sec per division. At least three electrical stimulations were given at random intervals of more than 1 min to avoid habituation. Latency and amplitude of the responses were recorded. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection of the signal baseline, and the amplitude was measured from peak to peak. The responses with the shortest latency and highest amplitude were evaluated. The response was considered absent if no consistent voltage change occurred using a sensitivity of 50 mV per division after three trials at maximum stimuli intensity.

While the participants were lying down and resting, RRIV was recorded by surface electrodes placed on the dorsum of each hand, and the ground electrode was put on one wrist. The bandpass was 10-100 Hz, the sensitivity was 100-200 μV per division, and the sweep speed was 100-200 msec per division. Using the triggering mode and delay line, the oscilloscope display was adjusted by the trigger sensitivity and sweep speed so that two QRS complexes were displayed on the screen. Responses were obtained both during rest and hyperventilation. Six deep inspirium-expirium cycles with 1 min intervals in between were established, and the results were recorded. Results were obtained for the longest RR interval duration (RR_{max}), for the shortest RR interval duration (RR_{min}) and for the mean RR interval duration (RR_{mean}). The RRIV was expressed as a percentage of the average RR interval using the following formula: $(RR_{max} - RR_{min}) \times 100/RR_{mean}$).

The sensation of vibration, the sensation of heat on the back of the foot, pinprick, and achilles reflex were evaluated over 10 points on both lower extremities by the NDS. A score ≥6 was considered abnormal.[8]

The SAS was used to assess the following autonomic symptoms: orthostatic, sudomotor symptoms, vasomotor, gastrointestinal, urinary, and sexual dysfunction. In the first part of the two-part questionnaire, the presence of the symptom was questioned as a yes or no response, while in the second part, the degree of severity of the symptom was graded between 1 and 5, with 1 being the least severe and 5 the most severe. The total score was calculated as 0-60 in males and 0-55 in females.[9]

Statistical analysis

All analyses were carried out with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The suitability of variables to normal distribution was examined with histogram graphics and the Kolmogorov-Smirnov test. While presenting descriptive analyses, mean, standard deviation, median, and minimum-maximum values were used. The Mann-Whitney U test was used to evaluate nonnormally distributed variables, between two groups, whereas the normally distributed variables were evaluated between more than two groups with analysis of variance. Spearman's correlation test was used to compare the measurement data. All p values <0.05 were considered statistically significant.

RESULTS

Demographic parameters and clinical background of the study groups are summarized in Table 1. There was no statistically significant difference between the groups in terms of age (p=0.081) and sex (p=0.075). The correlation was evaluated between age, sex, duration of colchicine use, and nerve involvement. A positive correlation was found between the duration of colchicine use and nerve involvement (polyneuropathy or carpal tunnel sydrome; p=0.002). A positive correlation was also found between age and nerve involvement (p=0.03) No correlation was found between sex and nerve involvement (p=0.921).

One patient from the AA amyloid-positive group was receiving peritoneal dialysis, and three of them were receiving hemodialysis. The mean duration of colchicine use in all patients participating in the study was 88.4±79.9 months. Colchicine use duration in the FMF amyloid-positive patient group was 132±81.3 months and 64.2±70.6 months in the amyloid-negative patient group. The difference was found to be statistically significant (p=0.016).

Nerve conduction studies (NCS) findings of the patient and control groups are shown in Table 2. In patients, it was evaluated that the median ulnar motor nerve latency value was longer, and the median ulnar motor amplitude value was lower. These results were statistically significant but were within the normal range and were not considered pathological. In NCS findings of the lower extremity in the patient groups, the mean sural latency value was longer, the mean sural conduction velocity was slower, and the difference was statistically significant.

Nerve conduction studies findings of amyloid-positive and amyloid-negative FMF patient groups are shown in Table 3. In the amyloid-positive FMF group, ulnar and radial sensory nerve median

Table 1. Demographic parameters and clinical background of the study groups

	Sex			Age distribution		SAS Q1A score		SAS Q1B score		NDS	
Groups	Male	Female	p	Mean±SD	p	Mean±SD	p	Mean±SD	p	Mean±SD	p
Amyloid-positive FMF	5	7		44.6±13.8		3.4±1.3		8.8±3.6		1.0±1.4	
Amyloid-negative FMF	14	20	0.07	35.9±8.6	0.08	2.7±2.0	0.22	7.9±6.3	0.47	0.2±0.8	0.14
Controls	11	19		38.4±10							

SAS: Survey of Autonomic Symptoms Scale; Q1A: First part; Q1B: Second part; NDS: Neuropathy Disability Score; SD: Standard deviation; FMF: Familial Mediterranean fever.

Table 2. The nerve conduction findings of the patient and control groups

Nerve	Study	Patients		Controls		*p*
		Median	IQR, 25th-75th percentile	Median	IQR, 25th-75th percentile	
	Latency (ms)	3.1	3.0-3.6	3.0	2.8-3.4	0.119
Median nerve (M)	Amplitude (μV)	14.2	12.8-16.8	14.2	10.9-18.1	0.978
	Conduction velocity (m/s)	57.7	54.9-63.3	61.5	55.2-65.0	0.142
	Latency (ms)	2.1	1.9-2.5	2.4	2.0-2.7	**0.042**
Ulnar nerve (M)	Amplitude (μV)	12.6	11.3-15.9	14.9	12.0-18.8	**0.044**
	Conduction velocity (m/s)	64.6	61.1-70.1	62.4	58.4-69.9	0.293
Median nerve (M)	F wave	24.8	23.6-26.6	23.5	22.3-24.6	**0.010**
	Latency (ms)	2.5	2.4-2.9	2.5	2.4-2.8	0.115
Median nerve (S)	Amplitude (μV)	30.1	18.7-38.5	29.3	25.5-35.5	0.708
	Conduction velocity (m/s)	51.1	44.8-55.1	53.2	46.5-57.0	0.188
	Latency (ms)	2.2	2.0-2.3	2.3	2.0-2.5	0.378
Ulnar nerve (S)	Amplitude (μV)	23.5	14.6-33.5	27.6	15.7-40.0	0.291
	Conduction velocity (m/s)	45.6	43.1-50.5	48.9	45.7-51.7	**0.055**
	Latency (ms)	2.3	2.1-2.5	2.3	1.9-2.6	0.775
Radial nerve (S)	Amplitude (μV)	11.1	8.1-16.8	12.0	8.5-16.3	0.624
	Conduction velocity (m/s)	54.8	49.5-59.0	51.5	19.1-60.3	0.749
	Latency (ms)	4.6	3.6-5.3	4.4	3.7-4.9	0.201
Tibial nerve (M)	Amplitude (μV)	12.5	9.4-15.3	11.2	7.5-15.7	0.512
	Conduction velocity (m/s)	44.7	42.9-48.2	46.3	43.8-49.9	0.157
Tibial nerve (M)	F wave	44.4	41.4-48.6	46.1	42.9-49.1	0.360
	Latency (ms)	3.4	3.1-3.7	3.3	3.0-3.6	0.470
Peroneal nerve (M)	Amplitude (μV)	7.9	6.7-9.2	6.4	5.4-7.7	0.962
	Conduction velocity (m/s)	56.0	53.3-58.5	56.4	52.-1.9	0.484
	Latency (ms)	3.2	2.7-3.5	2.5	2.4-2.9	**0.001**
Sural nerve (S)	Amplitude (μV)	11.5	8.6-16.1	13.1	11.0-16.1	**0.055**
	Conduction velocity (m/s)	44.5	40.3-51.0	55.8	48.8-60.5	**0.001**
	Latency (ms)	2.7	2.5-3.0	2.5	2.3-2.9	0.255
Superficial peroneal nerve (S)	Amplitude (μV)	10.8	8.9-13.4	11.6	9.6-15.1	0.257
	Conduction velocity (m/s)	50.8	44.4-54.7	51.6	46.4-61.3	0.220

IQR: Interquartile range; M: Motor; S: Sensory.

response amplitudes were lower, and the ulnar motor nerve conduction velocity was slower than the amyloid-negative FMF group. This difference was statistically significant. NCS findings of the lower extremity were not significantly different between the groups.

NCS findings consistent with polyneuropathy was detected in seven (15.21%) patients and carpal tunnel syndrome (CTS) in six (13.04%) patients. Six (50%) of seven patients with polyneuropathy were in the amyloid-positive group, and the remaining patient (2.94%) was in the amyloid-negative group. Five amyloid-negative patients and one amyloid-positive patient had bilateral mild CTS. The characteristics of patients with polyneuropathy and CTS and the scores of NDS and SAS are shown in Table 4. No anomaly was detected in nerve conduction studies performed in the control group.

Table 3. The nerve conduction findings of patients with and without amyloidosis

Nerve	Study	Amyloidosis (+)		Amyloidosis (–)		*p*
		Median	IQR, 25th-75th percentile	Median	IQR, 25th-75th percentile	
	Latency (ms)	3.1	3.0-4.0	3.1	3.0-3.5	1.000
Median nerve (M)	Amplitude (μV)	14.0	9.4-16.5	14.2	13.0-16.9	0.415
	Conduction Velocity (m/s)	58.9	50.6-63.8	57.7	55.2-62.4	0.945
	Latency (ms)	2.4	2.0-2.6	2.1	1.9-2.4	0.431
Ulnar nerve (M)	Amplitude (μV)	12.3	9.8-14.1	12.6	11.5-15.9	0.384
	Conduction Velocity (m/s)	62.4	57.1-65.3	66.2	61.6-70.8	**0.038**
Median nerve (M)	F wave	24.7	22.2-26.1	24.8	23.7-26.8	0.178
	Latency (ms)	2.5	2.3-2.9	2.5	2.4-2.9	0.629
Median nerve (S)	Amplitude (μV)	16.0	12.3-36.5	30.7	21.3-41.2	0.075
	Conduction Velocity (m/s)	51.1	45.2-57.0	51.3	44.3-55.1	0.689
	Latency (ms)	2.3	2.1-2.5	2.2	2.0-2.3	0.186
Ulnar nerve (S)	Amplitude (μV)	12.3	8.8-30.4	24.3	16.6-39.6	0.013
	Conduction Velocity (m/s)	43.9	41.3-47.8	46.3	43.9-51.0	0.121
	Latency (ms)	2.5	2.1-2.6	2.3	2.0-2.5	0.249
Radial nerve (S)	Amplitude (μV)	8.3	6.8-11.2	12.4	8.7-17.5	**0.012**
	Conduction Velocity (m/s)	54.8	47.9-61.2	54.6	49.6-58.9	0.989
	Latency (ms)	4.6	3.6-5.1	4.8	3.6-5.4	0.610
Tibial nerve (M)	Amplitude (μV)	12.1	6.3-13.0	13.0	9.8-16.2	0.102
	Conduction Velocity (m/s)	44.0	42.5-46.7	44.9	43.4-48.5	0.368
Tibial nerve (M)	F wave	44.4	40.8-48.5	44.7	41.9-48.8	0.617
	Latency (ms)	3.5	3.0-3.7	3.4	3.1-3.8	0.967
Peroneal nerve (M)	Amplitude (μV)	8.5	5.6-9.9	7.6	7. 0-9.2	0.189
	Conduction Velocity (m/s)	54.8	51.5-56.2	56.3	53.5-60.0	0.136
	Latency (ms)	3.3	1.9-3.4	3.1	2.7-3.7	0.758
Sural nerve (S)	Amplitude (μV)	7.7	4.4-12.0	11.8	9.4-17.7	0.570
	Conduction Velocity (m/s)	41.0	41.0-44.5	46.1	41.2-52.4	0.118
	Latency (ms)	2.6	2.5-3.1	2.7	2.5-3.0	0.450
Superficial peroneal nerve (S)	Amplitude (μV)	10.4	7.3-13.1	11.1	9.3-13.6	0.608
	Conduction Velocity (m/s)	49.4	42.2-54.9	50.9	44.8-55.0	0.535

IQR: Interquartile range; M: Motor; S: Sensory.

Palmar SSR could not be obtained in four (8.7%) patients, of whom two were in the amyloid-positive group and two were in the amyloid-negative group. Responses were obtained from all subjects in the control group. However, this difference was not statistically significant (p=0.149). Plantar SSR could not be obtained in 14 (30.4%) patients; three were in the amyloid-positive group, and 11 were in the amyloid-negative group. In the control group, five (16.7%) subjects had no plantar response. Results were not statistically significant (p=0.278).

When SSR was evaluated quantitatively, the mean plantar SSR amplitude value in the patient group was 820.09±757.11 μV and was significantly lower than in the control group (1283.29±1089.33 μV, p=0.041). There was no difference between latencies. No significant

Table 4. Characteristics of neuropathic involvement in patients

Sex	Age (year)	Neuropathy features	Amyloid presence	Dialysis treatment	SAS Q1A score	SAS Q1B score	NDS
Female	29	Sensory axonal PNP in the lower extremity	Present	Receiving	4	10	2
Female	54	Mild sensory axonal PNP in the lower extremity	Present	Receiving	5	13	2
Female	63	Sensory and motor axonal PNP in the lower extremity	Present	Not receiving	6	18	4
Male	38	Sensory axonal PNP in the lower extremity	Present	Receiving	4	11	0
Male	43	Sensory axonal PNP in the lower extremity	Present	Not receiving	3	9	2
Male	53	Sensory axonal PNP in the lower extremity	Present	Not receiving	1	3	2
Female	31	Mild CTS on the right	Absent	Not receiving	2	5	0
Female	45	Moderate CTS on the right and mild CTS on the left	Absent	Not receiving	2	6	0
Female	45	Bilateral mild CTS	Absent	Not receiving	5	15	0
Female	60	Mild CTS on the right	Absent	Not receiving	0	0	2
Male	34	Sensory axonal PNP in the lower extremity	Absent	Not receiving	1	4	2
Male	37	Mild bilateral CTS	Absent	Not receiving	3	8	0
Male	51	Mild bilateral CTS	Absent	Not receiving	0	0	0

SAS: Survey of Autonomic Symptoms Scale; Q1A: First part; Q1B: Second part; NDS: Neuropathy Disability Score; PNP: Polyneuropathy; CTS: Carpal tunnel syndrome.

difference was found between the two groups in terms of palmar SSR amplitude and latencies (Table 5). Furthermore, amyloid-positive and amyloid-negative patient groups showed no statistically significant difference (p>0.050). Additionally, we could not find any relationship between the groups in terms of age, duration of colchicine use, and SSR parameters (p=0.050).

RR_{max}, RR_{min}, RR_{mean}, and RRIV percentage values were compared between the groups during rest and hyperventilation. The RR_{mean} time R during rest and hyperventilation was significantly lower in the patient group compared to the control subjects (p=0.023, p=0.039). Although the mean of the RR_{max} was lower in the patient group, this value

Table 5. Evaluation of RRIV measurements between the patient and control groups

	Patients	Controls	
Parameter	Mean±SD	Mean±SD	*p*
Rest RR (ms)			
RR max	1112±502.5	1337±884.1	**0.051**
RR min	718.2±90.4	770±170	0.266
RR mean	824.8±104.2	897.6±176.6	**0.023**
RRIV %	33.1±33.5	34.0±24.4	0.484
Hyper-ventilation RR (ms)			
RR max	3434±455.0	4075.5±340.5	0.541
RR min	706.6±81.3	731±206.5	0.447
RR mean	997.4±239.1	1119±305.1	**0.039**
RRIV %	155.2±98.0	178.1±100.2	0.341

SD: Standard deviation; RRIV: RR interval variability; max: Maximum; min: Minimum.

was statistically near the limit of significance (p=0.051). Similarly, there was no significant difference between the amyloid-positive and the amyloid-negative patient groups in RRIV parameters (p> 0.050).

When RRIV was evaluated according to age, a negative correlation was observed during normal breathing in both groups. No statistically significant relationship was found between duration of colchicine use and RRIV in the patient group (p>0.050). In addition, no significant difference was determined between the amyloid-positive and the amyloid-negative groups in terms of NDS and SAS (p>0.050).

DISCUSSION

Although in primary amyloidosis, peripheral neuropathy and accompanying symptoms of autonomic neuropathy are frequently seen, it is not an expected finding to have peripheral nerve involvement in AA amyloidosis.[10] Even so, some case reports demonstrate that CTS can develop due to AA amyloidosis.[3,11] Autonomic nervous system involvement, particularly RRIV abnormalities, were reported in patients with complicated FMF at a progressive stage.[7,12]

The prevalence of CTS in our patient population (13.04%) was higher than in the general population (2.7%).[13] In a study of 88 pediatric patients in which colchicine-induced neuromyopathy was evaluated in FMF patients, CTS was detected in only one patient, and this condition could not be attributed to any cause.[14] Bademci et al.[3] demonstrated the accumulation of AA-type amyloid in a patient who was followed up for FMF and diagnosed as CTS clinically and electrodiagnostically. In this case, despite the absence of any systemic amyloidosis findings, the presence of amyloidosis was demonstrated in the rectal biopsy. In our study, one of six patients with CTS was in the amyloidosis group, and the remaining five patients had no systemic amyloidosis findings. As CTS may be a coincidental finding in these patients, it may be related to the toxic effect of colchicine treatment and even mark an undetectable amyloid accumulation since bilateral CTS was reported to be an early manifestation of systemic amyloidosis.[15]

In this study, one of the seven patients who had mild-moderate sensory axonal type polyneuropathy was in the amyloid-negative patient group, the rest were in the amyloid-positive group, and three of them were in a regular dialysis program. Considering that the cases of polyneuropathy due to AA amyloidosis are anecdotal in the literature, the underlying cause in these patients may also be the result of uremia. In addition, since all patients were undergoing colchicine treatment and the patients in the amyloid-positive group had a longer duration of colchicine use than in the amyloid-negative group, polyneuropathy findings in these patients may be associated with colchicine usage. However, in the literature, cases of neuropathy related to colchicine use has generally been reported as neuromyopathy.[16-18] In these cases, mild-moderate axonal polyneuropathy has been reported in addition to the myopathy findings and serum creatine kinase elevation. Although myopathy findings were not observed in our patients with polyneuropathy and their serum creatine kinase levels were normal, the relationship between polyneuropathy and amyloidosis or colchicine use could not be clarified. The longer duration of colchicine use and the higher incidence of neuropathy in AA amyloid-positive patients suggest that the development of neuropathy is associated with colchicine use rather than amyloidosis.

To our knowledge, there are no studies reporting SSR changes in FMF patients in the literature. Although SSR was elicited less in the patient group than in the control group in our study, the difference did not reach statistical significance. While SSR latencies did not make any significant difference between the groups, plantar SSR amplitudes were lower in the patient group (p=0.041). There was no statistically significant correlation between SSR latency and amplitude in regards to the presence of amyloidosis. Based on these results, we may suggest the presence of a subclinical sympathetic cholinergic dysfunction in FMF patients, but more data is needed on this subject. There is no consensus in the literature on how to evaluate SSR. However, it is considered that the qualitative evaluation made depending on whether there is a response or not is more objective and sensitive.[19] Latency and amplitude values, which are quantitative parameters, can

be affected by many variables.[20] Some authors do not recommend evaluating the amplitude because of the habituation and the variability in the measurements made in the same person.[21] However, we cannot say that these results are insignificant. Lower amplitudes were detected in patients with rheumatoid arthritis and systemic sclerosis, which are rheumatic diseases with autonomic nervous system involvement, compared to healthy volunteers.[22] In measurements made in patients with diabetes mellitus, a negative correlation was observed between the duration of diabetes and SSR amplitudes.[23] SSR amplitudes are also known to decrease with age. This difference is more pronounced in patients over 60 years old. Drory and Korczyn[24] reported that SSR could be elicited at a rate of 73% in the palm and 50% in the sole in a healthy population over 60 years old. In the present study, we found no correlation between age and SSR values, possibly due to the low number of cases and the mean age of the groups.

Although few studies suggest that cardiac involvement and autonomic dysfunction may be seen in FMF patients,[12,25] this study generally is in agreement with other studies that assessed RRIV among FMF patients. Nussinovitch et al.[26] compared the heart rate variability parameters of 34 amyloidosis-negative FMF patients with the same number of control groups and could not detect a significant difference between the groups. In the studies of Şahin et al.[27] and Kaya et al.,[28] the values of the patients and control groups were found to be similar. There are other studies with different methodologies in which RRIV is evaluated in FMF patients.[7,12,25-29] In a study of 55 patients designed to determine autonomic involvement in FMF patients, Rozenbaum et al.[12] showed that postural tachycardia syndrome, vasopressor or cardioinhibitory effects, or orthostatic hypotension were observed in 18.1% of patients. The authors stated that the cause was not clear. There are not enough studies on autonomic involvement in FMF patients, particularly with AA amyloidosis. In a study by Nussinovitch et al.[7] amyloidosis-positive FMF patients were examined in two groups as early stage (with proteinuria or nephrotic syndrome) and late stage (receiving renal transplantation or hemodialysis treatment). Patients with advanced-stage complicated AA amyloidosis had significantly lower values in favor of autonomic dysfunction. In the same study, no difference was found between the heart rate variability values of the amyloid-positive group and the control group, and this supported their previous studies. The mean RRIV and RR_{mean} values were lower in the patient group in our study. The mean RR_{max} value was lower in the patient group, but this value was statistically near the limit of significance. Moreover, we did not find any significant difference between the amyloid-positive and-negative groups between the RR variability values. One reason for this may be the low number of amyloid-positive patients. In addition, in the study of Nussinovitch et al.,[7] eight of 10 advanced amyloidosis patients were under immunosuppressive therapy due to renal transplantation, and two of them were on a hemodialysis program. In our study, one of 12 amyloid-positive patients was on peritoneal dialysis, and the other three were on hemodialysis treatment. The relatively fewer number of patients who were at the progressive stage in the amyloid-positive group and the lack of patients undergoing renal transplantation in our patient group may be the reason for no difference being detected between the amyloid-positive and-negative groups.

It has been shown in previous studies that RRIV decreases with age.[30] In our study, in accordance with the literature, a negative correlation was found between age and RRIV percentage ($p<0.001$). However, we did not find the same correlation in the measurements made during hyperventilation. Incompatibility with hyperventilation and physiological differences between individuals might be the reason for this.

This study has several limitations. The first limitation is the low number of amyloid-positive patients. The second limitation is the lack of biopsies demonstrating the presence of amyloidosis in patients in whom some changes in electrophysiological studies were detected, which would have allowed us to attribute these changes to amyloid deposition. Another reason that we could not attribute these changes to amyloid accumulation is that patients were taking colchicine as a treatment, which has a potential side effect on peripheral nerves.

Another limitation of our study is the selection of the control group from asymptomatic individuals. Although we excluded polyneuropathy in the control group with neurological examination, as expected, some individuals in the control group may have subclinical nerve involvement. Therefore, further studies need to involve more patients and controls.

In conclusion, the findings obtained in our study are insufficient to show that the development of amyloidosis in FMF patients leads to peripheral and autonomic neuropathy. Although they do not reach statistical significance, changes in SSR and RRIV parameters in the patient group may suggest the presence of subclinical dysautonomia in amyloid-positive FMF patients. However, further studies are needed to distinguish whether these changes are due to the direct effect of amyloid accumulation or variables such as drug use, disease duration, and age.

Ethics Committee Approval: The study protocol was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (date: 28.11.2017, no: 2017/514/118/6). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each participant.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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