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SYSTEMIC LUPUS ERYTHEMATOSUS AND FAMILIAL MEDITERRANEAN FEVER: A POSSIBLE ASSOCIATION

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Abstract

Systemic lupus erythematosus is one of the most common autoimmune disorders predominantly in women during their childbearing years. Any organ and system can be affected at this type of lupus. Familial Mediterranean fever is an autosomal recessively inherited disease that is characterized by self-limited attacks of fever and serositis. Serositis is a common symptom in both systemic lupus erythematosus and familial Mediterranean fever.

The objective of this study was to validate the possible association between familial Mediterranean fever and systemic lupus erythematosus and determine specifics of both diseases in case of their coexistence.

***Material and Methods:** The study enrolled: 23 patients with systemic lupus erythematosus and concomitant familial Mediterranean fever (group I); 23 familial Mediterranean fever patients (group II) and 23 patients with systemic lupus erythematosus (group III). Familial Mediterranean fever was established by molecular genetic testing of MEFV gene in all patients of both groups. All patients with systemic lupus erythematosus fulfilled diagnostic criteria of disease by American College of Rheumatologists. The investigation of patients involved compilation of demographic data (sex, age), medical history taking (age of disease onset, disease duration and previous treatment), as well as physical examination, disease activity estimation by Systemic Lupus Erythematosus Disease Activity Index, and laboratory data analysis.*

***Results:** Systemic lupus erythematosus coexisting with familial Mediterranean fever had mild course compared to classic cases of the specified diseases both in clinical and laboratory findings, including positive results for serum immunological markers of systemic lupus erythematosus: circulating immune complexes, anti-nuclear antibodies, anti-dsDNA and circulating immune complexes. To control activity of systemic lupus erythematosus and achieve disease remission low dose medication (prednisone, pulse-therapy or combined pulse-therapy) was required. The prevalent mutation was M694V (44.6%); V726A mutation composed 21.7%, M680I – 9.8%. The most common variations with M694V were the following: M694V/M694V, M694V/V726A, M694V/N.*

***Conclusion:** A remarkable overlap was highlighted between familial Mediterranean fever and systemic lupus erythematosus: both diseases have such common features as arthralgia, myalgia, arthritis, fever, skin involvement, serositis, hepatosplenomegaly and renal involvement. The MEFV mutations appear to modify systemic lupus erythematosus phenotype.*

***Keywords:** familial Mediterranean fever, systemic lupus erythematosus, MEFV mutations.*

Introduction

Systemic *lupus erythematosus* (SLE) is one of the most common autoimmune disorders in women during their childbearing years. In SLE any organ and system can be affected: skin involvement (erythema, "butterfly" symptom, discoid lesions, capillaritis, trophic disturbances), musculoskeletal system (arthralgia, myalgia, arthritis), pulmonary system (pneumonitis, pleuritis, discoid atelectasis), heart (pericarditis, endocarditis, myocarditis), gastrointestinal tract (abdominal crisis), kidneys (*lupus nephritis*), nervous system (epileptic seizures, cerebrovasculitis, stroke) [*Gaubitz M., 2006*].

Familial Mediterranean fever (FMF) is an autosomal recessively inherited disease that is characterized by self-limited attacks of fever and serositises (peritonitis, pleuritis, pericarditis). The disease is prevalent in Mediterranean region [*Livneh A. et al., 1997;*

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Lachmann H. et al., 2006]. Serositis is a common symptom in both SLE and FMF and may present as pleurisy, pericarditis or peritonitis. The first two pathology states are considered by the American College of Rheumatologists (ACR) as diagnostic criteria of SLE [*Tan E. et al., 1982*]. An increased prevalence of connective tissue systemic diseases has been reported in FMF [*Cattan D., 2005*]: seronegative spondyloarthropathies [*Langevitz P. et al., 1997; Balaban B. et al., 2005; Kasifoglu T. et al., 2009*], vasculitis, such as Behcet's disease [*Schwartz T. et al., 2000; Touitou I. et al., 2000*], Henoch-Schonlein purpura [*Gershoni-Baruc R. et al., 2003; Ozcakar Z. et al., 2008*], *polyarteritis nodosa* [*Ozen S. et al., 2001; Akar S. et al., 2005; Aksu K., Keser G., 2011*], juvenile idiopathic arthritis [*Rozenbaum M., Rosner I., 2004; Ayaz N. et al., 2009*], etc. Only several reports of SLE and FMF coexistence have been published [*Langevitz P. et al., 1995; 2002; Lidar M. et al., 2008; Yildiz G. et al., 2010; Shinar Y. et al., 2012*].

The objective of this study was to validate the possible association between FMF and SLE and determine specifics of both diseases in case of their coexistence.

Material and Methods

The study enrolled SLE patients with concomitant FMF (group I, n=23) and 2 comparison groups: one of them included only FMF patients (group II, n=23) and the other involved only patients with SLE (group III, n=23). The molecular-genetic investigation of MEFV gene allowed to establish FMF. All patients with SLE fulfilled diagnostic criteria of disease by ACR. The investigation of patients involved:

1. Compillation of demographic data (sex, age);
2. History taking, including early anamnesis of diseases: age of onset, disease duration/course, previous treatment;
3. Physical examination of patients;
4. Disease activity estimation using **S**ystemic **L**upus **E**rythematosus **D**isease **A**ctivity Index (SLEDAI) [*Lam G., Petri M., 2005*];
5. Analysis of laboratory data on:

- complete blood count, urinalysis (proteinuria, ‰); blood biochemistry analysis, including C-reactive protein (CRP), which was detected by latex-agglutination using appropriate kits ("Delta", Armenia, *mg/L*);
- immunological analyses of blood: circulating immune complexes (CIC); antinuclear antibodies (ANA), anticardiolipin antibodies (ACA), antibodies against double-stranded DNA (anti-dsDNA) detected by enzyme immune assay on "STAT FAX 2600" ("Awareness", USA) using commercial kits ("HUMAN", Germany, *IU/ml*); rheumatoid factor (RF) determined by latex-agglutination test ("Delta", Armenia, *mg/L*);
- molecular-genetic examination of MEFV gene localized on chromosome 16 by polymerase chain reaction (PCR) on "MRC Thermal Cycler" ("MRC", Germany).

For statistical analysis SPSS 16.0 (SPSS Inc., IBM Chicago, Illinois, USA) was used. Results for continuous variables were expressed as mean ± standard deviation and compared by Student's *t*-test. For comparing proportions of categorical parameters χ^2 (Chi-square) was used. Odds ratio (OR) was also estimated with 95% confidence interval (CI). The differences were considered significant at *p* value below 0.05.

Results

In each of the 3 groups there were 21 (91.3%) female and 2 (8.7%) male patients; age difference was statistically insignificant ($p>0.05$).

Mean age of patients in group I was 37.4±2.5 years, in group II it made 36.4±2.5 years and in group III – 35.6±2.6 years. Thus, all three groups were homogenous and comparable: there was no difference in sex and age. Mean age of the patients at the start of disease was as follows: in group I (we took into account the onset of both diseases: FMF and SLE) it was at 11.2±2.4 years and 21.2±2.2 years, respectively; in group II the beginning of FMF was at 9.3±2.2 years and in group III the beginning of SLE was at 26.9±2.6 years (Table 1).

The FMF onset in patients of group II (only FMF) was at an earlier age compared to cases of association

Table 1.

The mean age of patients at the beginning of the disease

Disease	Group I	Group II	Group III	*p*
familial Mediterranean fever	11.2 ± 2.4	9.3± 2.2	-	>0.05
systemic lupus erythematosus	21.2 ± 2.2	-	26.9±2.6	>0.05

with SLE. The age of SLE onset was similar in groups I and III. Duration of FMF in group I was 26.1±5.8 years, in group II – 26.9±5.8 years. Duration of SLE in groups I and III made 15.7±3.6 and 8.6±2.0 years, respectively. The difference in SLE duration between FMF accompanied cases and isolated disease was statistically significant ($p<0.05$).

We performed a comparative study on differences in clinical symptoms of both diseases, SLE and FMF, between groups. Clinical manifestations of FMF were compared with those in groups I and II (FMF-SLE and FMF), while SLE clinical symptoms were compared between groups I and III (Tables 2-3).

Attacks frequency more than 1 per month was significantly higher in group II (73.9%) than in group I (34.8%; $p<0.05$), while in group I attacks frequency less than 1 per month was recorded in 65.2% *vs* 4.3% in group II ($p<0.05$). Fever with body temperature of 38°C was observed in group I (78.3%) that was significantly more frequent than in group II (8.7%; $p<0.05$). Feverish temperature of 39°C, on the contrary, was more frequent in group II (69.6%) *vs* group I (17.4%; $p<0.05$). Abdominalgia, thoracalgia and arthralgia were the most common symptoms observed in almost all patients of both groups. Articular syndrome was manifested as mono- and polyarthritis. Monoarthritis was equivalent in both groups; recording rate was 50%. Polyarthritis was observed only in patients of group I (47.8%; $p<0.05$). There was no significant difference in splenomegaly, hepatomegaly and pleuritis manifestations in both groups. Attacks frequency of 1 per week, fever with body temperature of 40°C, pericarditis, aphthae were observed in solitary cases of both groups.

The frequency of SLE accompanying secondary antiphospholipid syndrome (APS) was significantly higher in SLE than in FMF-accompanied cases: 26.1% *vs* 4.3% ($p<0.05$). In concomitant FMF-SLE cases fever (38°C) was significantly

Table 2.

Clinical manifestations attributed to familial Mediterranean fever

Clinical manifestations	Group I		Group II		OR	95% CI	*p*	χ^2
	n	%	n	%				
attacks frequency: 1 per week	0	0	4	17.4	-	-	0.1	4.38
attacks frequency: more than 1 per month	8	34.8	17	73.9	5.3	1.4-18.8	0.01*	7
attacks frequency: less than 1 per month	15	65.2	1	4.3	0.02	0.003-0.2	0.001*	18.7
body temperature of 38°C	18	78.3	2	8.	0.03	0.005-0.1	0.001*	22.6
body temperature of 39°C	4	17.4	16	69.6	10.8	2.6-43.8	0.001*	12.7
body temperature of 40°C	1	4.3	4	17.4	4.6	0.4-45.08	0.3	2.02
abdominalgia	22	95.7	23	100.0	-	-	1.0	1.02
thoracalgia	15	65.2	23	100.0	-	-	0.004*	9.6
arthralgia	23	100	18	78.3	-	-	0.04*	5.61
monoarthritis	9	39.1	11	47.8	1.4	0.4-4.5	0.7	0.35
polyarthritis	11	47.8	0	0.0	-	-	0.001*	14.4
splenomegaly	14	60.9	13	56.5	0.8	0.2-2.7	1.0	0.09
hepatomegaly	6	26.1	11	47.8	2.5	0.7-8.9	0.2	2.3
pleuritis	14	60.9	11	47.8	0.5	0.1-1.9	0.5	0.7
pericarditis	4	17.4	0	0.0	-	-	0.1	4.3
skin rash	23	100	3	13	-	-	0.001*	35.3
aphthae	2	8.7	0	0.0	-	-	0.4	2.09

Note: * – statistically significant inter-group differences.

frequent in comparison with SLE ($p<0.05$). Articular syndrome manifested as arthralgia was described in all patients of both groups; monoarthritis was not revealed in any patient with SLE, but was described at FMF-SLE cases in 39.1% ($p<0.05$), whereas the frequency of polyarthritis was equivalent in both cases. In cases with FMF-SLE, splenomegaly was described in 60.9% ($p<0.05$). There was no significant difference in pericarditis, pleuritis and hepatomegaly frequency between the groups ($p>0.05$). All patients of both groups had various type of skin rash. "Butterfly" rash, photosensitivity, *livedo reticularis* were recorded more frequent than other manifestations. Trophic ulcers mainly described in concomitant APS were significantly more frequent in SLE cases: 34.8% *vs* 4.3% ($p<0.05$). The impairment of nervous system was observed only in SLE. Neither nervous system disturbance, nor cerebrovasculitis or strokes were seen in FMF-SLE cases (Table 3).

To estimate SLE activity SLEDAI was used as a specific disease activity index. In group I it made

Table 3.

Clinical manifestations attributed to systemic lupus erythematosus

Clinical manifestations	Group I		Group III		OR	95% CI	*p*	χ^2
	n	%	n	%				
antiphospholipid syndrome	1	4.3	6	26.1	0.1	0.04-0.5	0.006*	7.6
body temperature of 38°C	18	78.3	8	34.8	0.03	0.005-0.1	0.007*	8.8
body temperature of 39°C	4	17.4	7	30.4	2.07	0.5-8.4	0.49	1.07
body temperature of 40°C	1	4.3	0	0	-	-	1.0	1.02
arthralgia	23	100	23	100	-	-	-	-
monoarthritis	9	39.1	0	0	-	-	0.001*	11.1
polyarthritis	11	47.8	15	65.2	2.04	0.6-6.6	0.3	1.4
splenomegaly	14	60.9	5	21.7	0.2	0.04-0.6	0.01*	7.2
hepatomegaly	6	26.1	10	43.5	2.1	0.6-7.5	0.3	1.5
pleuritis	14	60.9	10	43.5	0.4	0.1-1.6	0.3	1.4
pericarditis	4	17.4	8	34.8	2.07	0.5- 8.4	0.49	1.07
skin rash	23	100	23	100	-	-	-	-
panniculitis	0	0	1	4.3	-	-	1.0	1.02
erythema	22	95.7	23	100	-	-	1.0	1.02
photosensitivity	17	73.9	20	87	2.3	0.5-10.8	0.5	1.2
livedo reticularis	14	60.9	15	65.2	1.2	0.3-3.9	1.0	0.09
capilaritis	4	17.4	10	43.5	3.6	0.9-14.1	0.1	3.7
Raynaud's phenomenon	6	26.1	7	30.4	1.2	0.3-4.4	1.0	0.1
alopecia	3	13	9	39.1	4.2	0.9-18.7	0.09	4.0
trophic ulcers	1	4.3	8	34.8	11.7	1.3-103.8	0.02*	6.7
aphthae	2	8.7	3	13	1.5	0.2-10.4	1.0	0.2
angiorethinopathy	4	17.4	8	34.8	2.5	0.6-10.04	0.3	1.8
mononeuropathy	0	0	1	4.3	-	-	1.0	1.02
polyneuropathy	0	0	2	8.7	-	-	0.4	2.09
cerebrovasculitis	0	0	8	34.8	-	-	0.004*	9.6
stroke	0	0	4	17.4	-	-	0.1	4.3
pneumofibrosis	0	0	2	8.7	-	-	0.4	2.09
pneumonitis	10	43.5	13	56.5	1.7	0.5-5.4	0.5	0.7

Note: * – statistically significant inter-group differences.

13.36±0.70, in group III – 22.04±2.20, which corresponded to high disease activity ($p<0.05$).

Studying data of laboratory findings on blood analyses we observed that mean erythrocyte sedimentation rate (ESR) was significantly higher in SLE in comparison with FMF-SLE – 23.2±2.2 *mm/h vs* 33.2±4.2 *mm/h* ($p<0.05$). The CRP mean level in group I was 28.08±4.80 *mg/L*, in group II it made 27.8±7.4 *mg/L* and in group III – 49.0±6.3 *mg/L*. Statistically significant difference ($p<0.05$) was revealed between groups I and III.

Urinalysis data revealed that proteinuria above 1‰ was more frequently described in group II (17.4%) *vs* groups I (0%) and III (8.7%) with significant difference ($p<0.05$, χ^2 -11.9). The mean level of urine protein in group I was 0.003±0.001‰, in group II – 0.3±0.1‰ and in group III – 0.33±0.10‰. Statistically significant difference was revealed between groups I and II, as well as between groups I and III ($p<0.05$).

In patients of groups I and III blood serum immunological analysis was carried out (Figure 1). It was revealed that in almost all patients of both groups RF was negative. Only in 1 SLE case it was positive. Levels of CIC, anti-dsDNA and ANA were significantly higher in SLE cases than in FMF-SLE ($p<0.05$). ACA was positive only in one FMF-SLE case.

In FMF and FMF-SLE patients molecular-genetic analysis of MEFV gene was carried out (Table 4).

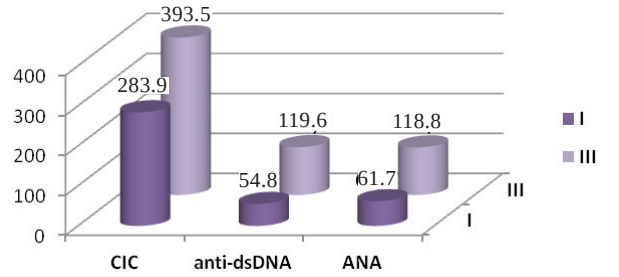

Figure 1. *Comparative analysis of immunological tests.*

In FMF-SLE cases of M694V/M694V and M694V/N were more frequent and composed 17.5%. In group II M694V/V726A combination prevailed making 39.1% *vs* 13.1% in group I. Thus, the most common mutations in FMF-SLE were M694V, M680I and V726A with different variations (Figures 2-3).

The prevalent mutation was M694V in 44.6%

Table 4.

MEFV mutations rate in patients with coexistence of familial Mediterranean fever and systemic lupus erythematosus and in familial Mediterranean fever patients

Mutations	Group I		Group II	
	n	%	n	%
E148Q/P369S	1	4.3	0	0
M680I/E148Q	1	4.3	0	0
M680I/N	2	8.7	0	0
M680I/V726A	1	4.3%	1	4.3
M694V/E148Q	2	8.7	1	4.3
M694V/M680I	1	4.3	3	13.1
M694V/ M694V	4	17.5	3	13.1
M694V/N	4	17.5	3	13.1
M694V/R761H	1	4.3	0	0
M694V/V726A	3	13.1	9	39.1
V726A/F479L	1	4.3	2	8.7
V726A/N	2	8.7	1	4.3

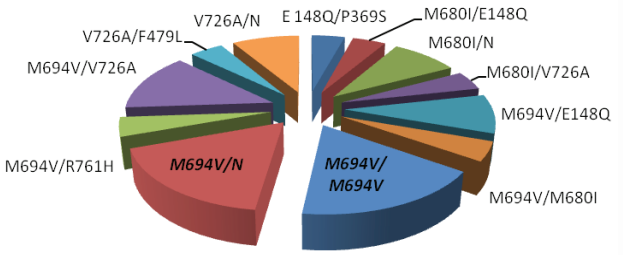

Figure 2. *MEFV combinations in cases with coexistence of familial Mediterranean fever and systemic lupus erythematosus.*

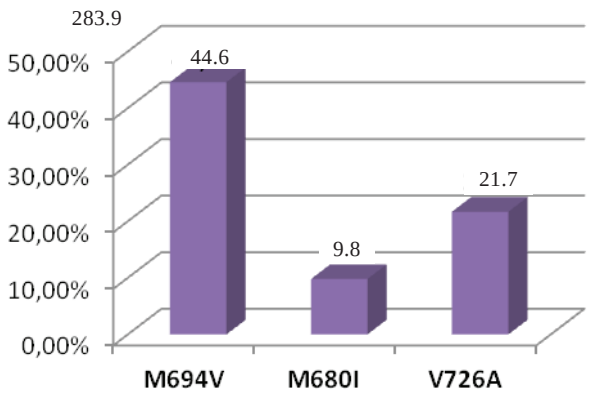

Figure 3. *The rate of most common mutations.*

Table 5.

Genotype-phenotype correlation in coexistence of familial Mediterranean fever and systemic lupus erythematosus

Clinical manifestations	M694V/ M694V			M694V/V726A			M694V/N			M694V/others		
	n	%	*p*	n	%	*p*	n	%	*p*	n	%	*p*
skin involvement	4	57.1	0.6	3	25	0.002*	4	57.1	0.6	4	50	0.4
articular syndrome	4	57.1	0.6	7	58.3	0.5	6	85.7	0.4	5	62.5	0.7
serositis	5	71.4	0.6	6	50	0.5	5	71.4	0.6	3	37.5	0.2
involvement of nervous system	0	0	0.6	0	0	0.3	0	0	0.6	0	0	0.2
antiphospholipid syndrome	0	0	0.4	0	0	0.2	0	0	0.4	0	0	0.4

Note: * – statistically significant inter-group differences.

cases. Most common combinations with M694V were the following: M694V/M694V, M694V/V726A, M694V/N (Figure 3). Correlation of most frequently revealed MEFV gene combinations (genotypes) with clinical manifestations of SLE was studied, in particular: skin involvement, articular syndrome, disturbance of nervous system, serositis, APS, proteinuria and SLEDAI.

Only one correlation was found between the most common variations of MEFV gene and clinical manifestations of SLE: M694V/V726A genotype was less frequently correlated with skin involvement ($p<0.05$) (Table 5).

No significant correlation was found analyzing the correlation between SLEDAI, proteinuria value and genotypes.

All patients with FMF-SLE received colchicine in mean dosage of 1-1.5 *mg/day*. In some cases to release inflammation and disease activity immunosuppressive drugs were required. In 38.7% cases there was no addition of cytostatics.

The patients of both groups received cyclophosphamide: 43.5% in group I and 56.5% in group II ($p>0.05$). In FMF-SLE group 17.4% patients used another immunosuppressive agent: azathioprine. Among patients with SLE 60.9% also received other immunosuppressive agents: azathioprine, mycophenolate mofetil, hydroxichloroquine. Likewise the case with FMF-SLE, azothioprine was the second frequent agent after cyclophosphamide taken by SLE patients (Table 6).

All patients of both groups were treated with glucocorticosteroids (GCS) (Table 7). The mean *per os* dosage of methylprednisone in FMF-SLE patients was 8.2±2.1 *mg/day* and in SLE patients – 18.5±2.2 *mg/day* ($p<0.05$).

To reduce inflammation and disease activity all SLE patients received combined pulse-therapy (intravenous injection of 1000 *mg* methylprednisone per day during three days with 1000 *mg* cyclophosphamide addition on the second day). Among patients with FMF-SLE 30.4% needed the combined pulse-therapy *vs* 100% amongst SLE patients. The difference between 2 groups was statistically significant ($p<0.05$).

Discussion

Coexistence of SLE and FMF seemed to have milder course than classic SLE and FMF, and lower dose medication (prednisone, pulse-therapy or combined pulse-therapy) was required to achieve control of SLE signs and symptoms. In comparison with FMF, attack frequency in FMF-SLE cases was less than 1 per month *vs* more than

Table 6.

Treatment with immunosuppressive agents

Medications	Group I		Group III		*p*	χ^2	OR	95% CI
	n	%	n	%				
cyclophosphamide	10	43.5	13	56.5	0.5	0.7	1.6	0.5-5.4
other immunosup/pressive agents	4	17.4	14	60.9	0.006*	9.1	7.3	1.8-28.9

Note: * – statistically significant inter-group differences.

Table 7.

Glucocorticosteroids-based treatment

Administration route	Group I		Group III		p	χ^2
	n	%	n	%		
intravenous	7	30.4	23	100	0.001*	24
per os	23	100	23	100	-	-

Note: * – statistically significant inter-group differences.

1 per month in classic FMF; body temperature at fever was 38°C *vs* 39°-40°C in FMF. Proteinuria was revealed in more FMF cases, and mean proteinuria values were significantly higher in FMF than in FMF-SLE combination.

Secondary APS was more frequently accompanying SLE than SLE-FMF, although the study of Y. Shinar and associates revealed that the frequency of secondary APS was equivalent among mutation carriers and non-carriers [*Shinar Y. et al., 2012*]. Disease activity by SLEDAI was significantly higher in SLE than in co-occurrence with FMF in contrast to report of the mentioned authors that SLEDAI did not differ significantly between the groups. Increased ESR and CRP values were also more frequently revealed in classic SLE. On the other hand, there are studies reporting that the existing high CRP values in FMF patients can be protective against SLE [*Ozen S. et al., 2005*]. Serological markers also were at higher titer in SLE *vs* SLE-FMF. Our results agree with published data that in FMF-SLE cases positive ANA and anti-ds-DNA are revealed at moderate titer [*Lidar M. et al., 2008; Yildiz G. et al., 2010*]. On the other hand, some studies failed to find any difference in serologic tests results between FMF patients and healthy people [*Hirschberg M., 1970; Flatau E. et al., 1989; Ben-Chetrit E., Levy M., 1990; Guler E. et al., 2012*].

Splenomegaly, monoarthritis were more frequent in cases of SLE-FMF than in SLE. Polyarthritis was revealed more frequently in case of FMF-SLE combination than in FMF cases.

Although arthritis in FMF is mainly manifested by acute attacks of monoarthritis [*Uthman I. et al., 2001; Lidar M. et al., 2005*], while in SLE it is presented by polyarthritis [*Cervera R. et al., 1993*], associated features may overlap in coexisting cases, making it impossible to establish the exact aetiology of a particular attack. Febrile episodes are common features of both diseases, though they tend to be of limited duration in FMF and more prolonged in SLE. Renal involvement, manifested by proteinuria, is the most severe complication of both diseases. In FMF it is manifested as amyloidosis, in SLE it is usually presented as glomerulonephritis. Renal biopsy is needed to understand the nature of renal involvement [*Ben-Chetrit E., 2003*].

A few cases of FMF-SLE association have been reported previously [*Bakir F., Saaed B., 1989; Turkmen M., Kavukcu S., 2002; Schreiber B. et al., 2008*]. In all mentioned studies the cases of SLE among FMF population were lower than expected. This trend for a lower incidence of SLE in FMF may be explained in part by underdiagnosis of SLE due to overlapping manifestations and a milder disease phenotype, when coexisting with FMF.

It is likely, that the moderation in disease phenotype and peculiar disease characteristics observed in patients with both SLE and FMF are related to MEFV mutation. According to study of Y. Shinar and co-authors, among 70 SLE patients 11 subjects were found to carry MEFV mutation: M694V, V726A and E148Q [*Shinar Y. et al., 2012*]. Our study revealed that the most common combinations of MEFV were as follows: M694V/M694V, M694V/V726A, M694V/N.

Thus, a remarkable overlap was highlighted between FMF and SLE: both diseases have such common features as arthralgia, myalgia, arthritis, fever, skin involvement, serositis, hepatosplenomegaly and renal involvement. Hence, our study suggests that SLE in FMF patients have milder disease spectrum. There is a considerable overlap between two diseases and MEFV mutations appear to modify the SLE disease phenotype.

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