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Seasonal residual activity in adult familial Mediterranean fever: a longitudinal observational study

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Abstract

Although it is assumed that cold exposure triggers inflammation in patients with familial Mediterranean fever (FMF), seasonal differences in FMF have not yet been investigated. This study aims to investigate the association of seasonal changes with the frequency of attacks, disease severity, and subclinical inflammation in FMF. This longitudinal study examined adult patients with FMF on an established treatment followed up for at least 1 year in Istanbul. Clinical characteristics, medications, intraseasonal attacks counts, arthralgia and arthritis, disease severity, and the subclinical inflammation parameters were recorded covering four seasons. Friedman's and Cochran's *Q* tests were used to analyze changes in the above-mentioned data over seasons. Additionally, all attacks experienced in each season were added, and interseasonal differences were compared with the Chi-square goodness-of-fit test. Data for 240 observations (60 patients) were analyzed. The mean age and disease duration were 39.78 (SD 11.91) and 10 (IQR 6–22.75) years, respectively. The comparison of medians for four seasons did not show any statistical differences in terms of attack frequency, disease severity parameters, markers of subclinical inflammation, and the presence of arthralgia and arthritis. The total number of intraseasonal attacks experienced by patients differed among the seasons ($p = 0.023$), with a higher count in winter. Adult individuals with established FMF are more likely to experience attacks in winter than summer, but this difference may not be seen in the general parameters of disease activity/severity. This result supports the notion that there is a pronounced residual activity in winter.

Keywords Familial Mediterranean fever · Seasons · Climate · Cold temperature · Arthritis

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of febrile peritonitis, pleuritis, and arthritis [1]. The FMF-associated *MEFV* gene mutation inhibits the anti-inflammatory function of the nonfunctional pyrin protein, causing uncontrolled inflammation. The most common finding is peritonitis, while other conditions include fever, pleuritis, arthritis, erysipeloid erythema, and myalgia. Treatment goals are to prevent and treat attacks, suppress subclinical inflammation between attacks, and prevent amyloidosis development. Colchicine is the drug employed for treatment. Patients are considered unresponsive if they have received the maximum tolerated dose of colchicine for at least 6 months, but still experience one or several attacks per month [2–4]. However, it is not yet known whether FMF displays seasonal variations and associated residual activity [5, 6].

A previous study on FMF found the most common triggering factors for serositis attacks as cold exposure (59.3%), emotional stress (49.8%), fatigue (40.0%), and menstruation (33.7%) [7]. However, it is unclear how cold exposure triggers inflammation in patients with FMF [8]. Furthermore, these studies have generally relied on patient-reported questionnaires for collecting data, and it is not objectively known whether patients have more frequent attacks in winter.

Patients with rheumatic diseases often claim the effects of seasonal changes on their disease [9]. In most parts of the world, the year is divided into four seasons (winter, spring, summer, and autumn), characterized by specific weather patterns (temperature, atmospheric pressure, humidity, and precipitation) and daylight hours [10]. Seasonal variations

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in disease have been studied for some rheumatic diseases, but have not been elaborated for FMF; only a few case reports emphasize seasonal effects in FMF. Several studies have reported seasonal variations in rheumatoid arthritis (RA) disease activity [11–13]. The climatic impact on RA is suspected to be mediated by factors such as temperature, humidity, sunlight, and atmospheric pressure. Evidence of seasonality has also been found for other autoimmune diseases [6].

Consequently, although some publications have supported the hypothesis that cold exposure is associated with recurrent FMF attacks depending upon the individual, it has not been documented whether disease activity, attack frequency, and subclinical inflammation differ by season. This study aims to investigate the association between seasonal changes and attack frequency, disease severity, and subclinical inflammation in adult patients with FMF that were followed up.

Methods

Patients

This longitudinal study included patients diagnosed with FMF according to Tel Hashomer criteria [14], at our outpatient clinic, monitored for at least 1 year between March 1, 2015 and 2020, regularly used colchicine at fixed doses, and who were given information on the number and time of attacks. In this cohort, patients with FMF were monitored at intervals of three months or more frequently, depending upon the clinical condition of patients. All patients were asked for the count of their attacks (and the date of each attack) in their last 3 months. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level results of patients between the attacks were also recorded every 3 months. All patients with these data available for the periods between specified dates were unselectively included in the study. For patients with multiple years of seasonal data (e.g., patients with regular 4-year follow-ups), the most recent data were used to avoid a selection bias. Exclusion criteria were the following: patients having an infection, pregnancy, breastfeeding, malignancies (or a history of malignancies), < 18 years old, psychotic diseases during the data collection period, and an FMF diagnosis of < 6 months prior. The study required a diagnosis period of > 6 months, so that participants could adapt to the disease and achieve stability in their medication use. This work was conducted in accordance with the Helsinki declaration and approved by the local ethics committee, with the approval date 02.10.2020 and number 09.2020.1083.

Data

Patient age, gender, the duration of disease, characteristics of attacks, treatment received, CRP and ESR levels, known presence of amyloidosis, and medication use were recorded. The number of attacks experienced since the last follow-up and the number of attacks that occurred in the relevant season were recorded to determine disease activity. Typical characteristics of the attacks were recorded to confirm whether the attacks were genuine. Disease severity was evaluated using the international severity scoring system for familial Mediterranean fever (ISSF) score [15] and Pras disease severity score (PrasS) [16]. CRP and ESR levels were used to estimate the presence of subclinical inflammation between attacks. Joint pain and arthritis detected during the physical examination were documented. 25-OH-D vitamin levels, which can vary by season, were recorded if available.

Seasons

Seasons were divided into autumn (September–November), winter (December–February), spring (March–May), and summer (June–August). In Istanbul, located in the northern hemisphere, these four seasons are distinguished by different characteristics [10]. Common Mediterranean climate features are seen in the city: it rains a lot and snows in the winter months, and summers are warm-hot and dry [17]. The above-mentioned data were recorded for patients for each season to allow comparison.

Statistics

In the descriptive statistical analysis, normally distributed data were evaluated with mean and standard deviation (SD), data with skewed distribution with median and interquartile range (25–75%), and dichotomous data with percentage distributions. The number of attacks experienced by patients during each season and their CRP levels, ESR, ISSF score, and PrasS between the attacks were compared using repeated measurements variance analysis or Friedman's test. The presence of arthralgia and arthritis during each season was compared with Cochran's Q test. To determine possible residual activity from the total data of patients, the number of attacks experienced during each season was totaled, and the total scores for four seasons were compared with the Chi-square goodness-of-fit test. Statistical significance was set at $p < 0.05$ in all analytical assessments. SPSS (statistical package for social sciences for Windows 21.0) software was used for statistical analysis of the study.

Table 1 Demographic and clinical characteristics of the patients with familial Mediterranean fever

Age, years	39.78 (SD 11.91)
Sex, female ratio	47 (78.3%)
Disease duration, years	10 (6–22.75)
MEFV gene mutation	
Homozygous	10 (16.7%)
Compound heterozygous	19 (31.6%)
Heterozygous	16 (26.6%)
Negative	4 (6.7%)
Unknown	11 (18.3%)
Amyloidosis ratio	5 (8.3%)
Dominant attack sign of the last years	
Peritonitis	42 (70%)
Fever	8 (13.3%)
Arthritis	7 (11.7%)
Pleuritis/pericarditis	3 (5%)
Attack features (ever)[a]	
Peritonitis	57 (95%)
Fever	39 (65%)
Arthritis	24 (40%)
Pleuritis/pericarditis	23 (38.3%)
Erysipelas-like erythema	9 (15%)
Treatment	
Colchicine	56 (93.3%)
Anakinra	1 (1.7%)
Canakinumab	3 (5%)
Colchicine dose, mg	1.5 (1.5–2)

Descriptive data are given with n (%), mean (SD), or median (25–75%)

MEFV Mediterranean fever, *SD* standard deviation

[a]Not a percentage of the total

Results

Patients

Of the 301 patients who met the diagnostic criteria during the specified 5-year period, 60 were recruited for the study according to the inclusion and exclusion criteria. Data for 240 observations were analyzed. Patients were excluded from the study due to insufficient follow-up period, irregular medication use (and associated attacks), unrecorded number of attacks for each season, pregnancy/breastfeeding, unstable disease and drug dose, ongoing infection in a given season, recent diagnosis, or a combination of these. Demographic, clinical, genetic, and treatment-related data of the patients are given in Table 1.

Seasonal differences of clinical data

The mean and median values of attacks experienced by the patients during the specified seasons, ISSF score, and PrasS did not display statistical differences (Table 2). The complaints of arthralgia and the presence of arthritis did not show any statistical difference among seasons ($p > 0.05$ for all). Markers of subclinical inflammation, including non-episodic CRP levels and ESR, were similar across seasons ($p > 0.05$ for both), while 25-OH-D levels were statistically low in winter ($p = 0.002$).

Patient distribution according to attack presence among seasons

Three patients had at least one attack in all four seasons and 13 had none. Among the remaining 43 patients, 19

Table 2 Seasonal differences of activity, complaints, subclinical inflammation, and vitamin D levels in patients with familial Mediterranean fever

	Autumn	Winter	Spring	Summer	*p*
Attack count (total), *n*	40	57	41	29	0.023
Number of attacks (per person)					0.268
Median (25–75%)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	
Mean (SD)	0.67 (1.17)	0.95 (2.04)	0.71 (1.20)	0.48 (0.95)	
ISSF (25–75%)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.853
PrasS (25–75%)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	0.895
Arthralgia (%)	13 (21.7%)	13 (21.7%)	19 (31.7%)	17 (28.3%)	0.212
Arthritis (%)	5 (8.3%)	7 (11.7%)	5 (8.3%)	6 (10%)	0.857
CRP, mg/L (25–75%)	3.12 (0–6.3)	3.13 (3–6.44)	3.17(3–4.9)	3.02 (0–4)	0.261
ESR, mm/h (25–75%)	24.5 (14–34.25)	23 (10–35)	21.5 (9.5–31)	20 (10.5–28)	0.669
25-OH-D, ng/L (25–75%) (n:32)	22.5 (18–28.75)	17 (13.5–23.75)	20.5 (15–26.75)	22.5 (17.5–32)	0.002

ISSF international severity score for FMF, *PrasS* Pras disease severity score, *CRP* C-reactive protein, *ESH* erythrocyte sedimentation rate

patients had autumn, 22 had winter, 19 had spring, and 16 had summer attack/attacks, or a combination of those.

Total attack frequency among seasons

The total number of attacks experienced by all patients was 40 in autumn, 57 in winter, 41 in spring, and 29 in summer (Fig. 1). The goodness-of-fit test showed a significant difference among the total number of attacks in four seasons ($p = 0.023$).

Discussion

While the results of this longitudinal study show no seasonal variations in activity/severity parameters (the average number of attacks per month, number of attacks for 3 months, and ISSF score) in patients with established FMF, they showed significant seasonal variations in the total number of attacks. The probability of encountering an attack increased in winter and decreased in summer. Furthermore, complaints of arthralgia, arthritis findings, and markers of subclinical inflammation did not differ across seasons. These results support the idea of the existence of a more pronounced residual activity in winter. From a professional's standpoint, although such information in a cross-sectional inquiry suggests that the disease is inactive, it also shows a probability of more frequent patient admissions for attacks in winter, requiring closer attention in questioning and following-up patients. This can help in developing better preventive strategies against triggers in winter from the perspective of the patient.

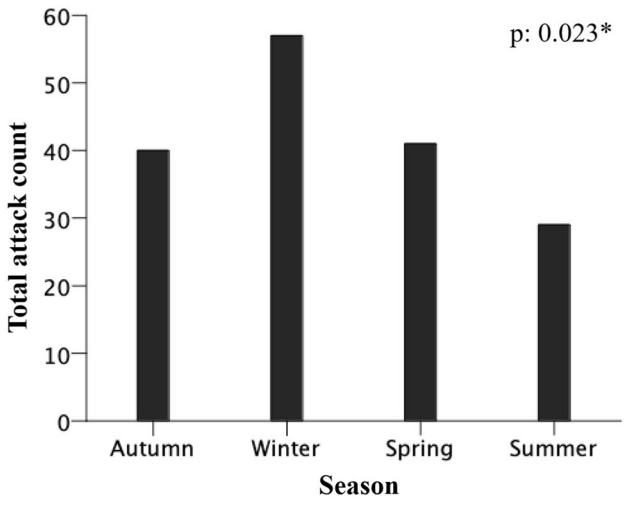

Fig. 1 The total number of attacks in each season: 40 in autumn, 57 in winter, 41 in spring, and 29 in summer. Chi-square goodness-of-fit test significance for equality: 0.023

Although no study has been conducted yet to examine seasonal variations in FMF, a few cases have been reported in the literature highlighting winter attacks or the impact of cold climate [5, 18]. Moreover, the cold is known to cause attacks in familial cold autoinflammatory syndrome (FACS) and some periodic syndromes [8, 19]. In previous studies, cold exposure has been identified as one of the significant triggers of FMF attacks [7, 20]. It has been reasoned that FMF attacks result from a balance disorder; thus, a minor inflammatory trigger can stimulate a severe response. The role of infections as triggers for FMF attacks is controversial [7], but a possible etiology associated with the seasonality of infection has not been ruled out [21]. Although our study excluded patients with active infections, further studies to investigate the effect of infections are warranted.

Most studies that investigated seasonal effects in some rheumatic diseases other than FMF have displayed activity variations associated with seasons. It has been reported that RA becomes more active in winter and spring [11, 13, 22], Behçet's disease is more active in autumn and spring [23], systemic lupus is more active in summer [24], systemic sclerosis worsens in winters [25], and gout attacks are more frequent in spring [26]. There has also been a study that reported no seasonal variation in psoriatic arthritis [27].

As recommended in the holistic approach, seasonal variations have been detected in studies investigating additional conditions (pain, fatigue, subclinical inflammation, etc.) other than activity parameters in rheumatic diseases. There are increasing studies on the importance of subclinical inflammation in FMF [28]. Subclinical inflammation markers evaluated by CRP and ESR in this study did not differ among the seasons. On the other hand, fatigue is more common in RA during the winter months [12]; patient complaints have been found to show seasonal variations without any change in the disease activity parameters in osteoarthritis, RA, and fibromyalgia [9]; and it has been argued that seasons affect pain parameters [29–31]. Although the primary design of our study was based on the occurrence of attacks and disease activity, secondary outcomes covered arthralgia, arthritis, and subclinical inflammation, but no seasonal differences were found.

Vitamin D levels, ultraviolet exposure, melatonin, and infections exhibit a pattern of seasonal variation [6]. Vitamin D levels might have affected the results of this study. The relationship between vitamin D levels and colchicine resistance has been reported in adult patients with FMF [32, 33], but seasonal variations have not yet been examined. A British study found that 13% of individuals with RA are deficient in vitamin D, and 50% have insufficient vitamin D levels during the winter months [34]. Likewise, another study found an inverse proportion in vitamin D levels and disease activity for autoimmune disease [6], but one study made this controversial [35]. This study included few patients with

data on vitamin D levels but observed seasonality in its levels similar to the number of attacks.

The strengths of this study include the use of a longitudinal design and follow-up data from the same patients that provided more reliable results. However, it has the following limitations: it has relatively small sample size, but a comparison of data from the same patients at different times improves the quality of statistical analysis. It has been conducted in a single region, and global studies are required to investigate the effects of climatic characteristics, pressure, and humidity. In addition, it might have been more accurate to evaluate the attacks of all patients in the same year, since there may have been seasonal changes between years. Furthermore, it did not include patients who were not under follow-up care. Patients who were not under follow-up care could be expected to display more exaggerated results, but this could have been accomplished with only patient questionnaires and would have yielded more subjective results. Another reason the study was limited to patients with the established disease was that FMF begins in childhood, and its course and the type of attacks may change over the years. Nevertheless, it is the first study in the literature to examine seasonal variations in adult or minor patients with FMF.

In conclusion, adult patients with established FMF are more likely to experience attacks in winter than in summer, but this difference may not be seen in the general parameters of activity. This supports the idea that there is a pronounced residual activity in winter. For rheumatologists, emergency room physicians, and family physicians, this means that cross-sectional inquiries may show the disease to be inactive, but there may be an increase in admissions due to attacks in winters. Therefore, careful patient follow-ups along with attentive inquiries in winter should be implemented. This also can aid in developing better preventive strategies against triggers in winter for patients.

Author contributions All authors worked on the study design, conception, data collection, analysis, interpretation of the data, statistical analyses, and manuscript writing. All authors were involved in drafting the article and revising it critically for important intellectual content. All authors are fully responsible for all aspects of the study and the final manuscript in line with the IJME 4 criteria. All authors approved the final version of the article. All co-authors take full responsibility for the integrity and accuracy of all aspects of the work. No part of the manuscript has been copied or published elsewhere in whole or in part.

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Data availability The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability The code used to analyze the current study is available from the corresponding author on reasonable request.

Declarations

Conflict of interest Authors declare no conflict of interest, financial support, or relationships.

Ethics approval This retrospective cohort study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Marmara University Ethics Committee approved this study. The approval date and number were 02.10.2020 and 09.2020.1083, respectively. The manuscript has not been copied or published elsewhere in whole or in part.

Consent to participate Not applicable.

Consent to publication Not applicable.

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