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ORIGINAL ARTICLE

Detection of Familial Mediterranean Fever attacks by using a connected activity tracker and assessment of impact of attacks to daily physical activities: a pilot study

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Abstract

Objective The objective of this study was to assess the impact of Familial Mediterranean Fever (FMF) attacks on daily physical activity and detect FMF attacks using a connected activity tracker.

Methods Patients with FMF according to the Tel-Hashomer criteria were included in this prospective observational study. Attack-related data were collected weekly via phone call to avoid memory bias. Median steps in attack and attack-free days were calculated and compared using the Wilcoxon rank test. Sensitivity and specificity threshold for capturing attacks was set to two thirds of median steps per day in the whole observation period.

Results Twelve patients participated in the study. The median age of patients was 26 (18–32) years, and 7 (58.3%) of them were male. Patients with attacks ($n = 10$) walked a median of 6990 (4552–11,531) steps per day in attack-free days, whereas this number decreased to a median of 1841 (590–4783) steps in attack days ($p = 0.005$). The activity tracker captured 42 of 45 attack days and 312 of 361 attack-free days. The cutoff value had 93% sensitivity and 86% specificity for capturing attacks.

Conclusions FMF attacks significantly impair the physical activity of patients. Activity tracking may be a reasonable method to document FMF attacks. This might prevent errors due to memory bias and help accurately identify and treat patients with FMF.

Keywords Activity tracking · Biosensor · Familial Mediterranean Fever · Wearable technology

Introduction

Familial Mediterranean Fever (FMF) is a recessively inherited systemic auto-inflammatory disease characterized by recurrent febrile episodes of sterile peritonitis, pleuritis, arthritis, and erysipelas-like rash [1–3]. FMF is diagnosed by a set of clinical criteria [4] and associated with mutations in the MEFV gene [5, 6], which is located on chromosome 16p13.3 and encodes the pyrin protein. Malfunctioning pyrin as a result of MEFV gene mutation results in overproduction of interleukin (IL)-1β, which is the principal cytokine that drives attacks in FMF [7]. Clinical presentation of FMF can be variable; the type, intensity, and complications of attacks can differ across populations and mutations [8]. However, typical FMF attacks are usually short-lived, lasting 1–3 days, and mostly devastating and exhausting. Patients are frequently symptom-free between attacks. Musculoskeletal conditions like enthesopathy [9], exercise myalgia [10], osteitis [11], and arthralgia [12] are often noted on the legs and quite common but usually overlooked or ignored by patients. Febrile and painful FMF attacks and musculoskeletal features of disease may decrease daily activity.

Although attacks are mostly self-limited, FMF is associated with impaired quality of life and work productivity and may be complicated with secondary amyloidosis, which is the most common cause of mortality in patients with FMF [13]. The goals of FMF treatment are the prevention of attacks and secondary amyloidosis and improvement in quality of life. Colchicine is the standard of care for FMF treatment because it reduces the risk of amyloidosis and improves quality of life by reducing the frequency, duration, and severity of attacks [14, 15]. Nonetheless, 5–10% of patients do not respond well to colchicine even at the maximum tolerable doses. Although

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there is no consensus on the definition of inadequate response to colchicine to step-up/alternate the treatment, attack frequency despite the maximum tolerable doses of colchicine is the most widely used parameter for adjusting treatment [15–17]. While there is no gold standard test for detecting FMF attacks, attack frequency is usually assessed by the declaration of the patient during visits, which is subject to significant memory bias. Moreover, attack diaries are left blank most of the time. The lack of any gold standard test for attack detection and memory bias could easily affect the treatment process. More accurate methods for detection of attacks and identification of resistant patients who are candidates of more expensive and potentially more hazardous treatments are of crucial importance.

Physical activity including everyday walking and aerobic exercise may be objectively and longitudinally assessed using connected activity trackers. It is shown that flares of rheumatoid arthritis (RA) and axial spondyloarthritis (Ax Spa) can be detected with activity tracking [18]. Besides the flares of RA and Ax SPA, serosal attacks of FMF result in bed confinement, and musculoskeletal attacks cause significant pain upon exertion. When the attacks resolve, patients completely return to their regular activities. Even mild-severe febrile attacks and musculoskeletal features of the disease may reduce daily routine activities and can be easily captured by activity trackers. The primary objective of this study was to assess the impact of FMF attacks on daily physical activities using a connected activity tracker. The secondary objective was to assess the capability of activity tracking in indirectly determining the frequency, severity, and duration of FMF attacks.

Methods

Patient selection and demographic data

This prospective observational study was conducted in the Rheumatology Clinic of Gazi University Hospital, which is a tertiary care center. Patients aged > 18 years and had a definite diagnosis of FMF according to the Tel-Hashomer [4] criteria and declared frequent FMF attacks (more than once in a month, also commonly defined as colchicine resistant FMF [crFMF]) were included in this study if they had a smartphone and agreed to use a connected activity tracker. Demographic and disease characteristics, current treatments, and MEFV gene mutations were recorded. All patients continued to use a maximum tolerated dose of colchicine as their treatment and were candidates for interleukin-1 (IL-1) inhibitor treatments. The local ethics committee approved the study and informed consent was obtained from all participants.

Activity tracker

Each patient received a Jawbone® activity tracker and was instructed to wear it continuously during the study period. The Jawbone tracker records the number of steps per hour, day, week, and month and was validated previously [19]. Patients were not instructed on their regular daily activities. Activities and whether the patients wore the device were tracked daily through the supplied mobile application of Jawbone®. Physical activity was defined as the number of steps taken per day.

Collecting activity and attack data

All attack-related data were collected weekly by phone conversation to avoid memory bias. FMF attacks were assessed by asking patients, "Have you experienced any FMF attack during the last week, if yes, in which days?" Then attack days were recorded for each patient. If an activity decline was observed in patient-reported attack-free days, patients were further questioned for possible reasons and musculoskeletal features of the disease like myalgia, arthralgia, and bone pain. Daily physical activity data of each patient was collected from the software named Up®, which was developed by Jawbone (available in Play Store and App Store). Figure 1 presents the data collection process obtained from three patients.

Statistics

The data were analyzed using "Statistical Package for the Social Sciences (SPSS) for Windows" version 15.0 (SPSS Inc., Chicago, IL) and Microsoft Excel®. Categorical data were presented as numbers (%) and continuous data as median (minimum–maximum), unless stated otherwise. Steps attained in attack days and attack-free days were calculated for each patient and compared using the Wilcoxon rank test. A p value ≤ 0.05 was considered statistically significant.

For each patient, two thirds of their own median steps per day in the whole observation period was defined as the cutoff point for detection of attacks. Daily step numbers less than this value were determined separately and named as "low step day." If they were greater, they were named as "high step day." Low step days were compared with the patient-reported attack days, and it was determined whether attack days matched with low step days. The crosstabs feature was used to determine the sensitivity and specificity of the cutoff point. Sensitivity was defined as the ability of a "low step day" to cover FMF attack days. Specificity was defined as proportion of overlap between "high step day" and attack-free days.

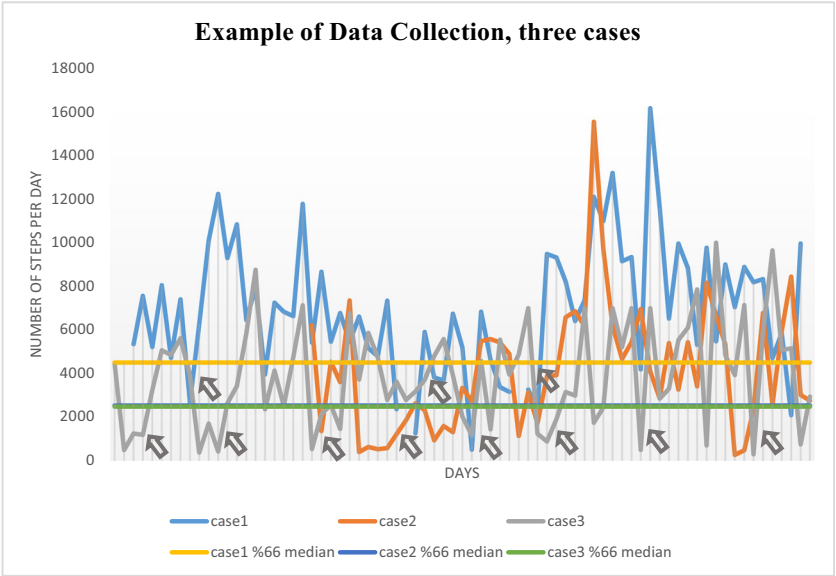

Fig. 1 Data collection process of three cases. Arrows indicate the attacks of patients

Results

A connected wearable device was offered to 16 patients; 15 of them agreed to enroll in this study. Three patients were excluded due to incompliant use of devices. Finally, data of 12 patients were analyzed. The median age of participants was 26 (18–32) years, and 7 (58.3%) of them were male. The median disease duration was 13 (3–25) years. Ten patients harbored homozygous or compound heterozygous (8 patients, M694V/M694V; 2 patients, M694V/M680I) exon 10 *MEFV* mutations, while two patients had single heterozygous (M694V/-). Table 1 shows the demographic data of patients.

While the total number of days after the patients enrolled in this study was 514, the number of days that patients wore the activity tracker was 452 (88%). The mean activity tracker used was 37.7 ± 21 days for a single patient. Ten patients reported at least one attack in the observation period, while two patients had none. Patients reported 28 separate attacks with a total duration of 45 days. Majority of the attacks lasted 1 day (68%), and 18% of the attacks lasted for ≥ 3 days. In the overall assessments of 10 patients with an attack, the median number of each patient's steps per day was 6893 (3731–11,501). Patients walked a median of 6990 (4552–11,531) steps per day in attack-free days, while this number decreased to a median of 1841 (590–4783) steps in attack days. This decrease in daily physical activity was statistically significant ($p = 0.005$) (Fig. 2). When patients were grouped according to MEFV mutations (M694V/M694V, M694V/M680I, and M694V/-), we found impaired daily physical activity in all groups. The median steps per day decreased from 5917 (3731–8822) to 1537 (590–4537) in the M694V/M694V group, from 9635 (7770–11,501) to 4218 (3654–4783) in the M694V/M680I group, and from 5345 (3921–6771) to 1590 (1089–2092) in the M694V/- group during attacks. However, only the M694V/M694V group showed statistical significance ($p = 0.02$, $p = 0.18$, and $p = 0.18$, respectively). Every single attack resulted in decreased steps ($p = 0.005$). The average step decrease ranged from 1576 to 9733 per day, which corresponds to a 33–84% relative decrease during attack days.

Table 1 Patient's demographics and disease characteristics

	$N = 12$
Age, years	26 (18–32)
Male	7 (58%)
Age at FMF diagnosis, years	15.5 (2–24)
Disease duration, years	13 (3–25)
Fever	58%
Peritonitis	92%
Pleuritis	83%
Arthritis	67%
Erysipelas-like erythema	25%
Myositis	25%
Maximum tolerated colchicine dose, mg	2 (1–2.0)

All parameters are presented as median (min–max) or number (%) unless indicated

Detection of FMF attacks via median steps per day

For each patient, two thirds of their own median steps per day in the whole observation period were defined as the cutoff point, and the capability of the activity tracker to capture attacks was assessed. Days on which the number of steps was less than the cutoff value were matched with patient-reported attack days and vice versa. Through this cutoff point, the activity tracker captured 42 of 45 attack days and 312 of 361

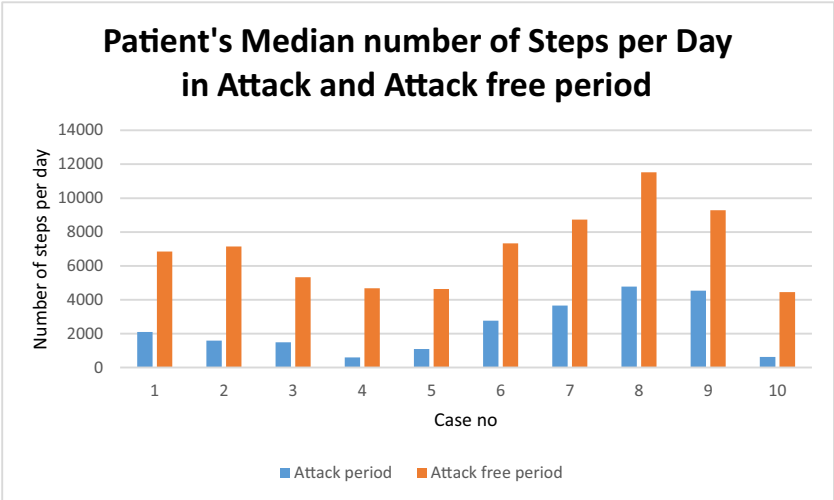

Fig. 2 Comparison of patient's median number of steps per day in attack and attack-free period

attack-free days and had 93% sensitivity and 86% specificity for determining attacks. The positive predictive value of the cutoff point for the presence of attacks was 46%, while the negative predictive value was 99%.

Discussion

In this study, we tracked patients with a wearable device and obtained attack information weekly from the patient. We assessed the impact of FMF attacks on daily physical activities and determined that FMF attacks negatively affect the patient's daily physical life and daily physical activity tracking could be a reasonable method to indirectly determine the frequency, severity, and duration of FMF attacks. We also found that the impact of attacks on physical activity may vary in patients with different mutations. We noted that all attacks significantly decreased physical activities by 33 to 84% irrespective of attack duration. Our results provide further insights into the use of wearable technology for capturing flares of diseases.

Tracking disease activity is of vital importance in the management of chronic diseases and has a key role in making treatment decisions. Monitoring of disease activity of chronic diseases, which manifest as episodes or attacks such as FMF, gout, and migraine, is performed with either paper based or electronic disease diaries during visits. Although these diaries seem to be practical, patients with complete well-being between the attacks may not give much importance to this and are not adherent to fill them properly. Eventually, evaluation of these patients is performed by patients' own statements, which may have a significant memory bias. Smart wearable devices may help to overcome all these limitations.

Wearable devices emerged as activity monitors or life coaches (steps, sleep time, burned calories, etc.) and widely used at present due to their reliability in measuring steps with their accelerometer sensors [20, 21]. Biosensor and wearable technologies are developing incredibly fast, and it is a reality that they will be used in daily clinical practice soon [22]. For disease follow-up, the idea is simply tracking a person's daily activity pattern and detecting inactive state inconsistent with the patient's routine. Information gathered in this manner may help determine the health impairments of the person. Daily activity is a mutual parameter for all humans, and tracking daily activity may also help compare the impact and severity of different diseases with heterogeneous manifestations.

FMF is a periodic disease characterized by recurrent self-limiting inflammatory febrile attacks of serositis, arthritis, and erysipelas-like erythema. FMF attacks, particularly serositis involving the peritoneum and pleura with extremely severe and crippling pain, usually cause bed confinement. After the attacks resolve, patients completely return to their routine. Severe attacks are observed as an acute sharp decline in daily routine activity of the patient in the activity monitor. In the same way, mild or moderate attacks decrease daily activities according to the type and severity of attacks. Therefore, we used the daily step counts to capture attacks and defined a simple cutoff point, which showed significant sensitivity and specificity. Moreover, FMF is an example of an episodic disease with great inter-individual differences, and our study on activity tracking might constitute a model for monitoring patients with these episodic disorders.

The strength of our study includes the fact that it is the first study that used activity tracking as a disease activity tool in FMF and showed its reliability. Moreover, the impact of attacks on daily physical activity was shown. This study may be considered as a pilot study showing that episodic diseases like FMF may be managed with activity tracking.

This study has some limitations. The major limitation is the inclusion of a relatively small number of patients. We only included patients with crFMF with frequent attacks in our study to shorten the waiting time for the occurrence of attacks.

Colchicine-responsive patients and healthy subjects were not included. Because of the small sample size, the subgroup analysis had less power. As a result of this, although there is a significant numerical change in median steps per day in all three groups of patients according to the MEFV gene mutations, only those in the M694V/M694V homozygous group were reflected in the *p* values. Therefore, we cannot conclude whether there is a difference between patients with different MEFV gene mutations or colchicine responses and resistance on their activity impairment. Further studies with large sample size should be conducted to determine whether there is a difference in the impact of attacks on daily physical life between patients with different mutations or colchicine responses. Since intense activity may trigger attacks [23], some patients with FMF may prefer a sedentary lifestyle. We determined the reasons for low activity days in our study and found that some patients moved less at weekends or days on leave, probably because they woke up late. Physicians must be aware of this while evaluating patients in daily clinical practice. The study has potential pitfalls about wearable technology such as patient compliance [24].

FMF attacks significantly impair the physical activity of patients. Activity tracking may be a reasonable method to capture and document FMF attacks. Hence, this might prevent errors due to memory bias, help identify and precisely treat those patients resistant to conventional treatments, and confirm patients who declare frequent attacks. Our study may constitute a model for capturing attacks of other episodic diseases such as gout or migraine.

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Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Disclosures None.

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