Clinical Neurophysiology 130 (2019) 1358–1363

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

It twitches without kicking – An association between fragmentary myoclonus and arousal?

Karin Trimmel *, Gerald Lindinger, Marion Böck, Andrijana Stefanic, Gerhard Klösch, Stefan Seidel

Department of Neurology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

ARTICLE INFO

Article history:
Accepted 2 May 2019
Available online 1 June 2019

Keywords:
Fragmentary myoclonus
Polysomnography
Periodic limb movements
Cohort study
Arousal

HIGHLIGHTS

- Fragmentary myoclonus (FM) is a polysomnographic feature of unknown significance.
- We analyzed 200 polysomnographies in a mixed sleep disorder patient cohort.
- FM is ubiquitous and most frequent in older men but may relate to sleep fragmentation in women.

ABSTRACT

Objective: Fragmentary myoclonus (FM) is a polysomnographic motor phenomenon of unknown clinical relevance. This study investigates FM prevalence, gender differences, sleep stage distribution and association with clinical factors using recently introduced advanced FM scoring criteria.

Methods: We analyzed polysomnographic recordings of 178 patients of a mixed sleep-disorder patient cohort. FM indices (FMI) of newly introduced 25 µV (FMI25) and standard 50 µV (FMI50) amplitude cut-offs were calculated.

Results: FMI25 and FMI50 were higher in men compared to women. FMI were higher during wakefulness and lower during S3 compared to all other sleep stages, with stronger effects in men compared to women. FMI25 was correlated with higher age, lower mean oxygen saturation, lower sleep efficiency, higher periodic limb movement (PLM) index, shorter sleep period time and higher arousal index. Linear regression showed that age predicted higher FMI25 in both males and females. Additionally, higher arousal index predicted higher FMI25 in women only. FMI were not associated with the presence of sleep-related breathing disorders.

Conclusions: We suggest FM represents a ubiquitous motor phenomenon occurring spontaneously during relaxed wakefulness and sleep, primarily in men and with advanced age.

Significance: In women, particularly FMI25 may be a surrogate marker for more frequent arousals and sleep fragmentation.

1. Introduction

Fragmentary myoclonus (FM) is a surface electromyographic phenomenon recorded during polysomnography (PSG), resulting in invisible or hardly visible irregular twitches or jerks in an asymmetrical fashion over both sides of the body (Broughton and Tolentino, 1984). The fragmentary myoclonus index (FMI) is used as a scoring method for the quantification of FM (Lins et al., 1993). Excessive FM (EFM) was first described by Broughten and colleagues in 1985 in a mixed cohort of patients with sleep disorders, and an association with various disorders such as obstructive sleep apnea syndrome (OSAS), periodic limb movement disorder

Abbreviations: AHI, Apnea/hypopnea index; ANOVA, Analysis of variance; BMI, Body mass index; EFM, Excessive fragmentary myoclonus; EMG, Electromyogram; FM, Fragmentary Myoclonus; FMI, Fragmentary myoclonus index; FMI25, Fragmentary myoclonus index using 25 µV amplitude cutoff; FMI50, Fragmentary myoclonus index using 50 µV amplitude cutoff; HFLM, High frequency limb movements; ICSD, International Classification of Sleep Disorders; IQR, Interquartile range; LM, Limb movements; OSAS, Obstructive sleep apnea syndrome; PLM, Periodic limb movements; PLMD, Periodic limb movement disorder; PSG, Polysomnography; RBD, REM sleep behavior disorder; RLS, Restless legs syndrome; SD, Standard deviation; SPT, Sleep period time; TWT, Total wake time.

* Corresponding author.
E-mail address: karin.trimmel@meduniwien.ac.at (K. Trimmel).

https://doi.org/10.1016/j.clinph.2019.05.011
1388-2457/

(PLMD), narcolepsy and insomnia were reported (Broughton et al., 1985). EFM was introduced in the International Classification of Sleep Disorders (ICSD) in 1990 and is defined as at least five FM events per minute for a period of at least 20 min of NREM sleep (American Sleep Disorders Association, 1990). A pathological FMI for the whole night, on the other hand, has not been defined (American Academy of Sleep Medicine 2005; Frauscher et al., 2011; American Academy of Sleep Medicine 2014). Frauscher and colleagues could recently demonstrate a 100% prevalence of FM in a mixed cohort of 62 sleep lab patients, with 95% of patients presenting with an FMI of 3-292, and suggested a mild association of FM with sleep-related breathing disorders (Frauscher et al., 2011). However, the clinical relevance and underlying (patho-) physiological mechanisms of FM remain poorly explored, and high FM prevalence was also demonstrated in healthy subjects (Frauscher et al., 2014).

Recently, Hoque and colleagues (2013) challenged the existing criteria for scoring of FM events during polysomnography, underlining the necessity to include the analysis of sleep stage distribution of FM as well as the application of a lower amplitude criterion for FM of 25 μV, as compared to the previously used 50 μV amplitude cut-off criterion (Broughton and Tolentino 1984; Lins et al., 1993).

The aim of this study was to investigate the prevalence of FM in relation to sleep stages and possible associations with clinical factors using the recently introduced advanced scoring criteria (Hoque et al., 2013).

2. Methods

2.1. Patients

For this study, all-night polysomnographic recordings of all consecutive patients who presented with sleep disturbances between January 1st 2011 and December 31st 2013 at our sleep lab at the Department of Neurology were analyzed. Prior to every PSG, each patient had been seen by a sleep expert of the Department of Neurology and a comprehensive semi-structured interview on the general and sleep history has been taken.

Six of 206 recordings were excluded from this study due to incomplete PSG and/or clinical data. Hence, we included 200 recordings of a total of 178 patients (63.5% males) in this study who underwent a full-night PSG. Twenty patients had two consecutive PSG-nights and three patients had three consecutive PSG recordings.

This study was approved by the local ethics committee of the Medical University of Vienna. Due to the retrospective nature of the study no written informed consent prior to study participation was obtained.

2.2. Video polysomnography

All subjects underwent at least one night of video PSG according to standard protocols suggested by Rechtschaffen and Kales (1968). Recordings were initiated between 10:00 p.m. and 10:45 p.m. for an 8-h duration. PSG included electroencephalography (EEG; C3 and C4 with M1 and M2 as reference electrodes), electrooculography (vertical and horizontal eye movements), EMG (mental, both anterior tibialis muscles), and cardiorespiratory recording (single channel electrocardiography, pneumoflow, respiratory movements from induction plethysmography, and transcutaneous oxygen saturation).

Sleep was scored according to Rechtschaffen and Kales (1968). For scoring of electromyographic (EMG) activity, bipolar surface EMG was recorded with the low-pass filter at 35 Hz, the high pass filter at 10 Hz, and a sampling rate of 100 Hz. Amplification was set at 5 μV per mm for scoring of REM-related EMG activity, and at 10 μV per mm for scoring of isolated limb movements (LM), periodic LM (PLM), high frequency LM (HFLM), and FM. Impedance of surface EMG electrodes had to be lower than 10 kΩ. LM and PLM were scored according to the Atlas Task Force of the American Sleep Disorders Association (1992).

2.3. Fragmentary myoclonus

FM were scored visually according to Lins et al. (1993) and the extended criteria by Hoque et al. (2013) as muscle surface potentials of the anterior tibialis muscles with an amplitude of 25–200 μV (Hoque et al., 2013) or 50–200 μV (Lins et al., 1993) and a duration of less than 150 msec. To quantify FM, the FMI was calculated by averaging the total number of FM potentials per hour of the respective sleep stage (S1, S2, S3, S4, REM) for both the 25–200 μV amplitude criterion (FMI25) and the 50–200 μV amplitude criterion (FMI50). For practical reasons and better comparability with polysomnographic studies using the American Academy of Sleep Medicine (AASM) sleep scoring criteria (2014), sleep stages S3 and S4 were merged into one for the current analysis. EFM was scored according to AASM standards (2014; presence of at least five FM events per minute for a period of at least 20 minutes of NREM sleep).

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS 25.0 for Windows. All data were tested for normal distribution using the Kolmogorov-Smirnov test. According to distribution of data, Wilcoxon signed rank test was used for analyses of paired groups and Mann-Whitney U-test in case of two groups. Correlation analyses of FMI with age, body mass index (BMI), apnea/hypopnea index (AHI), mean oxygen saturation, sleep period time (SPT), total wake time (TWT), sleep latency, sleep efficiency, arousal index, periodic limb movement (PLM) index, and presence or absence of sleep-relevant medication (benzodiazepines, antidepressants, antipsychotics, anticonvulsants, or dopaminergic drugs) were performed using Pearson or Spearman correlation coefficients according to distribution of data. Comparison of correlations between groups was performed using Fisher's Z transformation (http://vassarstats.net/rdiff.html). Linear regression analyses were performed using FMI25 and FMI50 as dependent variables, and variables that were significant in the correlation analyses as predictors. Comparison of regression coefficients between groups (males vs. females) was performed creating dichotomous dummy variables and interaction terms with the predictors for separate multiple regression analyses (Pothoff 1966; Weaver and Wuensch 2013).

Repeated analyses of variance (ANOVA) were calculated based on a 5 (Sleep stage; Wakefulness/S1/S2/S3/REM) × 2 (Amplitude criterion; 25 μV/50 μV) repeated ANOVA design with "Gender" as a between factor using Greenhouse-Geisser correction of p-values. Post-hoc comparisons were performed using Bonferroni correction. For the repeated ANOVA and linear regression analyses, non-normally distributed variables were naturally log-transformed. A significance level of $p < 0.05$ was applied to all analyses.

3. Results

3.1. Demographics

Demographic characteristics of the whole patient population are shown in Table 1. Sleep apnea (43.8%) was the most prevalent

Table 1
Demographic characteristics of all patients (n = 178) and patient subgroups. Age is presented as mean and SD and BMI is presented as median and IQR.

	All	Sleep apnea	Insomnia	RLS/PLMD	Hypersomnia	Parasomnia	RBD
n (%)	178 (100)	78 (43.8)	38 (21.3)	42 (23.6)	11 (6.2)	7 (3.9)	2 (1.1)
Gender (f/m)	65/113	17/61	21/17	18/24	4/7	5/2	0/2
Age (mean and SD)	52.7 (16.4)	57.2 (13.0)	49.1 (16.7)	55.2 (16.6)	35.6 (11.6)	28.0 (12.1)	73 (1.4)
BMI (median and IQR)	27.0 (8.0)	30.0 (8.0)	25.0 (6.0)	27.0 (5.0)	22.0 (10.0)	22.0 (7.0)	28.5 (n.a.)
Sleep-relevant medication (yes/no)	71/107	23/55	17/21	23/19	4/7	2/5	2/0

BMI = body mass index, IQR = interquartile range, RBD = REM sleep behaviour disorder, RLS/PLMD = restless legs syndrome/periodic limb movement disorder, SD = standard deviation.

sleep disorder, followed by restless legs syndrome/periodic limb movement disorder (RLS/PLMD; 23.6%), insomnia (21.3%), idiopathic hypersomnia and narcolepsy (6.2%), non-REM parasomnias (3.9%) and REM sleep behavior disorder (RBD; 1.1%). Results based on PSG-recordings and according to the different sleep pathologies are shown in Table 2. All patients reached sleep stages S1 and S2. Stage S3 was reached by 96.1% of patients and REM sleep stage was achieved by 92.1% of patients. Further details on the distribution of diagnoses can be seen in Table 1. Results based on PSG recordings are displayed in Table 2 and the distribution of sleep stages by the different patient groups can be found in Table 3.

3.2. Frequency of FM and gender differences

FMI25 could be found in all patients, with a median FMI25 of 24.56/h (range: 1.33/h–267.20/h). The occurrence of FMI50 was significantly lower (4.94/h, ranging from 0/h–192.09/h; $Z = -11.22$, $p < 0.001$). Compared to women, men had significantly higher FMI25 (median 24.44, IQR 54.97 vs. median 18.14, IQR 26.50; $U = 2.262$; $p < 0.001$) and FMI50 (median 6.47, IQR 16.75 vs. median 2.43, IQR 5.53; $U = 2.268$; $p < 0.001$, Figs. 1 and 2).

3.3. Effects of sleep stage

Repeated ANOVA revealed a significant main effect of amplitude criterion, with higher FMI25 compared to FMI50 ($F(1,179) = 815{,}07$, $p > 0.001$), independent of gender and sleep stage (Fig. 3). Furthermore, there was a main effect of sleep stage ($F(2.572,460.468) = 63.02$, $p < 0.001$, $\varepsilon = 0.643$; Fig. 3). Post-hoc analyses of pairwise comparisons (Bonferroni-corrected) indicated higher FMI (independent of amplitude criterion) during wakefulness as compared to sleep stages (all $p < 0.001$), and lower values during S3 as compared to all other sleep stages and wakefulness (S3 vs. awake and S2: $p < 0.001$; S3 vs. S1 and REM: $p < 0.05$; Fig. 3). Additionally, there was a significant interaction effect of Sleep stage × Gender, with stronger effects in men compared to women ($F(2.572,460.468) = 4.71$, $p = 0.005$, $\varepsilon = 0.643$, Fig. 2). There was also an interaction effect of Sleep Stage × Amplitude criterion, with stronger effects for FMI50 compared to FMI25 ($F(2.987,534.637) = 3.75$, $p = 0.01$, $\varepsilon = 0.747$; Fig. 3).

3.4. Correlation of FM indices with clinical factors and gender differences

Across all patients, there was a significant association of higher age ($r = 0.41$, $p < 0.001$), lower mean oxygen saturation ($\rho = -0.23$, $p = 0.001$), shorter SPT ($\rho = -0.18$, $p = 0.01$) longer TWT ($\rho = 0.17$, $p = 0.02$), lower sleep efficiency ($\rho = -0.27$, $p < 0.001$), longer sleep latency ($\rho = 0.16$, $p = 0.02$), higher arousal index ($\rho = 0.15$, $p = 0.03$), and higher PLM index ($\rho = 0.24$, $p = 0.001$) with higher FMI25. Apart from the arousal index, these effects remained significant for FMI50 (Table 4). Comparison of correlation coefficients

Table 2
Polysomnographic parameters of all PSG recordings (n = 200) across all subjects and for patient subgroups.

	Total	Sleep Apnea	Insomnia	RLS/PLMD	Hypersomnia	Parasomnia	RBD
n (%)	200	96 (48)	40 (20)	42 (21)	11 (5)	9 (5)	2 (1)
SPT (min)	421.5 (64)	425 (65)	420 (116)	421.3 (69)	431.5 (50)	401 (37)	400.3 (n.a.)
TWT (min)	32 (7)	32.3 (43)	38.5 (77)	33.5 (55)	16 (19)	32 (41)	57.2 (n.a.)
Sleep latency (min)	23.5 (41)	28 (41)	28 (61)	23.5 (57)	12 (20)	21 (38)	51 (n.a.)
Sleep efficiency (%)	79 (83)	77 (22)	84 (19)	78 (23)	93 (9)	90 (08)	63 (n.a.)
AHI	4.72 (14.5)	13.3 (19.7)	1.12 (4.8)	2.2 (4.6)	0.6 (2.6)	0.15 (0.5)	13.3 (n.a.)
Mean SaO_2 (%)	94 (2)	94 (3)	95 (3)	94 (2)	95 (3)	96 (1)	94 (n.a.)
Arousal Index	14.4 (13.0)	16.8 (14.1)	11.3 (10.1)	17.2 (12.8)	10.3 (4.3)	7.5 (3.3)	11.0 (n.a.)
PLM Index	1.33 (7.06)	1.5 (7.0)	0.5 (3.6)	6.8 (11.4)	0 (0.9)	0 (0.6)	0.2 (n.a.)

AHI = apnea/hypopnea index, SaO_2 = arterial oxygen saturation, SPT = sleep period time, TWT = total wake time.

Table 3
Number (percentage) of patients reaching sleep stages S1, S2, S3, and REM in the whole patient cohort as well as in the different patient groups.

	Wake	S1	S2	S3	REM
Insomnia	38 (21.3%)	38(21.3%)	38(21.3%)	37 (20.8%)	35 (20.0%)
OSAS	78 (43.8%)	78 (43.8%)	78 (43.8%)	74 (41.6%)	71 (39.9%)
RLS/PLMD	42 (23.6%)	42 (23.6%)	42 (23.6%)	40 (22.5%)	39 (21.9%)
Narcolepsy/Hypersomnia	11 (6.2%)	11 (6.2%)	11 (6.2%)	11 (6.2%)	11 (6.2%)
RBD	2 (1.1%)	2 (1.1%)	2 (1.1%)	2 (1.1%)	2 (1.1%)
Parasomnia	7 (3.9%)	7 (3.9%)	7 (3.9%)	7 (3.9%)	7 (3.9%)
Total	*178 (100%)*	*178 (100%)*	*178 (100%)*	*171 (96.1%)*	*165 (92.7%)*

OSAS = obstructive sleep apnea syndrome; RBD = REM sleep behaviour disorder, RLS/PLMD = restless legs syndrome/periodic limb movement disorder.

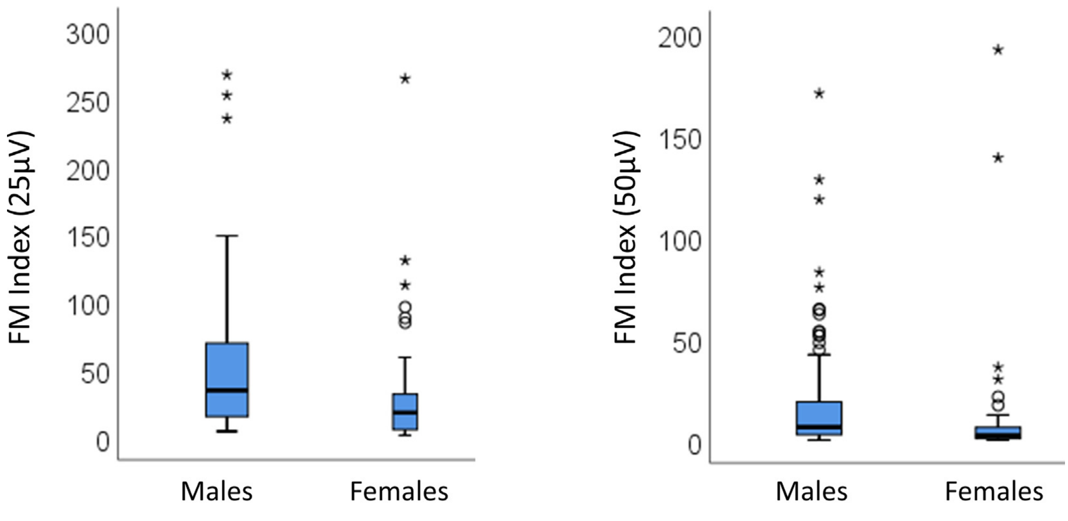

Fig. 1. Fragmentary myoclonus (FM) Indices are significantly higher in men than women. Left: FMI25. Right: FMI50. Note the different scales for the two FM indices. Boxes represent median and IQR, whiskers represent range, circles represent outliers and asterisks are extreme outliers. FMI25 = fragmentary myoclonus index using 25 µV amplitude cut-off, FMI50 = fragmentary myoclonus index using 50 µV amplitude cut-off, IQR = interquartile range.

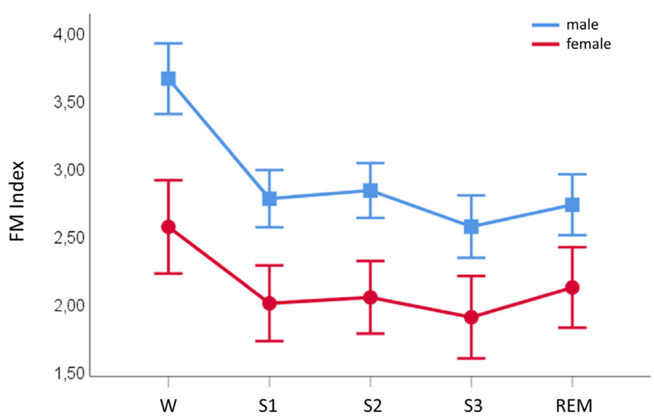

Fig. 2. Results of repeated measurements ANOVA. Distribution of FM indices in males (blue) and females (red) over the different sleep stages. Shown are mean and 95% CI. ANOVA = analysis of variance, FM = fragmentary myoclonus, CI = confidence interval, W = wakefulness, S1 = stage 1 sleep, S2 = stage 2 sleep, S3 = stage 3 sleep, REM = rapid eye movement sleep.

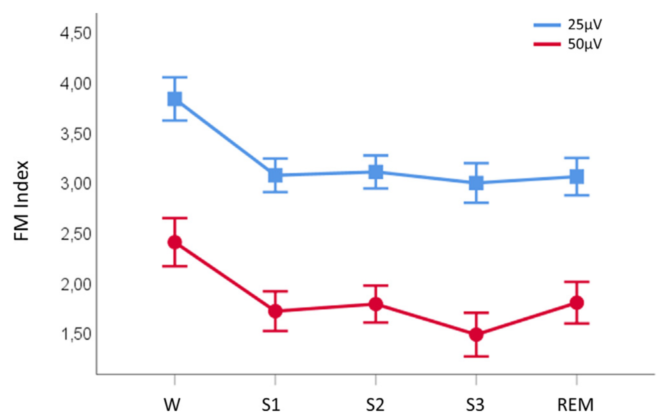

Fig. 3. Results of repeated measurements ANOVA. Distribution of FMI25 (blue) and FMI50 (red) over the different sleep stages. Shown are mean and 95% CI. W = wakefulness, S1 = stage 1 sleep, S2 = stage 2 sleep, S3 = stage 3 sleep, REM = rapid eye movement sleep. ANOVA = analysis of variance, CI = confidence interval, FMI25 = fragmentary myoclonus index using 25 µV amplitude cut-off, FMI50 = fragmentary myoclonus index using 50 µV amplitude cut-off.

revealed stronger correlations of FMI25 with the arousal index in females compared to males (p = 0.02). Additionally, there was a stronger relation of FMI with the AHI in women, although correlations across groups remained non-significant (Table 4). There was no correlation of FMI25 ($r = 0.01$, p = 0.85) or FMI50 ($r = -0.03$, p = 0.70) with presence or absence of sleep-relevant medication (benzodiazepines, antidepressants, antipsychotics, anticonvulsants, or dopaminergic drugs).

3.5. Linear regression

All variables that were significant in the bivariate correlation analyses (age, SPT, O2-saturation, TWT, sleep efficiency, sleep latency, arousal Index, PLM Index) were used as predictors for FMI in a linear regression model.

3.5.1. FMI25

In males, age (beta = 0.26, p = 0.02) and SPT (beta = −0.42, p = 0.004) were significant predictors of higher FMI. In females, age (beta = 0.44, p = 0.02) and the arousal index (beta = 0.55, p = 0.007) were significant predictors. Comparison of regression coefficients indicated stronger predictive values of the arousal index in women as compared to men (beta = 0.74, $p = 0.01$), whereas there was no difference in regression coefficients for age (beta = 0.34, $p = 0.11$) or SPT (beta = −0.59, $p = 0.21$).

3.5.2. FMI50

In males, linear regression indicated a significant effect of shorter SPT for a higher FMI (beta = −0.32, p = 0.03). In females, no significant effects were observed. Intergroup comparisons for SPT showed no difference of regression coefficients between males and females (beta = −0.11, $p = 0.38$).

3.6. Association with sleep-related breathing disorders

There was no difference in FMI25 between females with (median 19.24, IQR 37.02) or without sleep-related breathing disorders (median 14.34, IQR 25.28; $U = 598$, $p = 0.32$) and between males with (median 35.51, IQR 54.43) or without sleep-related breathing disorders (median 34.19, IQR 59.96; $U = 1890$, $p = 0.68$).

Table 4
Correlation of FMI25 and FMI50 with sleep variables. Pearson's r is presented for age and Spearman's rho is presented for all other variables according to distribution of data. For comparison of males vs. females, Fisher's Z transformation was applied. Significant results ($p < 0.05$) are highlighted in bold.

	FMI25			FMI50			males vs. females FMI25 (*p*)	males vs. females FMI50 (*p*)
	All patients r/ρ (*p*)	Males (n = 128) r/ρ (*p*)	Females (n = 72) r/ρ (*p*)	All patients r/ρ (*p*)	Males r/ρ (*p*)	Females r/ρ (*p*)		
Age	**0.41 (<0.001)**	**0.18 (0.04)**	**0.36 (0.002)**	**0.35 (<0.001)**	0.13 (0.15)	0.12 (0.31)	0.19	0.94
BMI	0.8 (0.29)	−0.02 (0.82)	0.12 (0.32)	0.7 (0.32)	−0.02 (0.81)	0.12 (0.31)	0.35	0.35
AHI	0.11 (0.14)	−0.10 (0.26)	**0.28 (0.02)**	0.05 (0.49)	−0.14 (0.13)	0.18 (0.13)	**0.01**	**0.03**
O2-	Saturation	−**0.23 (0.001)**	−0.12 (0.17)	−**0.26 (0.03)**	−**0.19 (0.01)**	−0.11 (0.21)	−0.15 (0.20)	0.33
0.79								
SPT	−**0.18 (0.01)**	−**0.24 (0.01)**	−0.12 (0.32)	−**0.20 (0.01)**	−**0.21 (0.02)**	−0.22 (0.07)	0.41	0.94
TWT	**0.17 (0.02)**	0.16 (0.07)	**0.26 (0.03)**	**0.17 (0.02)**	0.12 (0.19)	**0.30 (0.01)**	0.48	0.21
SE	−**0.27 (<0.001)**	−**0.18 (0.05)**	−**0.37 (0.001)**	−**0.25 (<0.001)**	−0.17 (0.06)	−**0.29 (0.01)**	0.17	0.40
SL	**0.16 (0.02)**	0.16 (0.08)	**0.28 (0.02)**	**0.17 (0.02)**	0.12 (0.19)	**0.31 (0.01)**	0.40	0.18
Arousal Index	**0.15 (0.03)**	0.02 (0.81)	**0.35 (0.003)**	0.08 (0.29)	0.04 (0.69)	**0.25 (0.03)**	**0.02**	0.15
PLM Index	**0.24 (0.001)**	0.13 (0.14)	**0.35 (0.003)**	**0.21 (0.002)**	0.13 (0.15)	**0.26 (0.03)**	0.12	0.37

AHI = apnea/hypopnea index, BMI = body mass index, FMI25 = fragmentary myoclonus index using 25 μV amplitude cut-off, FMI50 = fragmentary myoclonus index using 50 μV amplitude cut-off, PLM = periodic limb movement, SE = sleep efficiency, SL = sleep latency, SPT = sleep period time, TWT = total wake time.

Accordingly, there was also no difference in FMI50 between females with (median 3.38, IQR 4.44) or without sleep-related breathing disorders (median 2.28, 5.62; $U = 533$, $p = 0.87$) and between males with (median 6.34, IQR 24.61) or without sleep-related breathing disorders (median 8.08, IQR 15.95; $U = 1882$, $p = 0.65$).

4. Discussion

Our study on FM in the largest sample of patients with sleep disorders to date showed that FM appeared in every patient confirming previous reports of FM in smaller cohorts as an omnipresent phenomenon in physiological and pathological sleep in both patients (Frauscher et al., 2011, 2014) as well as healthy controls (Frauscher et al., 2014). It has previously been suggested that only EFM, defined by an arbitrary cut-off of five FM potentials per minute over a duration of 20 min (Broughton et al., 1985), is pathological. However, the frequency of EFM was very low in our cohort (3.9% of patients using FMI25, 0% using FMI50).

FM has rarely been studied in larger samples and its clinical relevance remains unclear. An association with sleep-related breathing disorders has been suggested (Frauscher et al., 2011), which was not confirmed in our cohort for both FMI cutoffs. Although there was a moderate correlation of FMI with the mean oxygen saturation across all subjects, it did not withstand multivariate testing. Furthermore, there was no difference in median FMI values after dichotomizing the sample into patients with and without sleep-related breathing disorders.

Men had significantly higher FMI compared to women, and FMI increased with age independently of gender, which is in accordance with previous investigations (Auer et al., 2018; Frauscher et al., 2011). We also found an association of higher FMI with shorter sleep duration, longer total wake time, lower sleep efficiency, higher arousal index and higher PLM index, of which only the association with arousal index remained significant in the multivariate analysis, with stronger effects in women compared to men, and a more pronounced effect for FMI25 compared to FMI50.

Multivariate testing indicated a specific pattern of distribution of FM across sleep stages, with highest FM indices during wakefulness, followed by REM sleep and S1 and S2 sleep, and lowest values in S3. This effect was more pronounced in men compared to women. A decrease of FM from light to deep sleep and higher values during REM sleep is in line with previous investigations (Montagna et al., 1988; Frauscher et al., 2011). Of note, the few foregoing studies investigating the nighttime distribution of FM did either not include an analysis of FM during wakefulness (Lins et al., 1993; Frauscher et al., 2014), or showed similar FM-frequencies during wakefulness compared to REM sleep (Montagna et al., 1988; Frauscher et al., 2011), and neither included different FMI amplitude cutoffs. Hence, our observation of significantly higher FM incidence during wakefulness is of crucial importance which might stem from the larger number of subjects we studied in comparison to previous investigations and supports the view that FM is associated with arousal.

Interestingly, in women, higher FMI were associated with higher arousal indices. Early investigations in healthy subjects suggest that REM sleep is accompanied by a significant increase in sympathetic nervous activity, while REM twitches are followed by abrupt short reductions of sympathetic nervous activity (Somers et al., 1993). One could speculate that more frequent FM in women with higher arousal indices might counterbalance the overactive sympathetic nervous system that is known to be related to more frequent arousals (Amihăesei and Mungiu 2012).

The physiological origin of FM is still of debate. The observation of high occurrence of FM during wakefulness as well as REM sleep, representing the sleep period of greatest inhibition of tonic muscle activity, seems paradox. Electrophysiological studies in cats suggest that this may be explained by the different nature of motoneurons being responsible for myoclonic twitches and for those involved in tonic muscle activity, and that myoclonic jerks represent the phasic response of a supraspinal system, overwhelming the inhibitory influence of other supraspinal systems (Gassel et al., 1964). Early studies in neurological patients confirmed this concept of phasic reticulo-spinal volleys of descending alpha motoneurons (Dagnino et al., 1969). Furthermore, it has been discussed that FM represents a spectrum of motor phenomena, ranging from simple fasciculations to more complex and protracted movement patterns (Montagna et al., 1988). This is in line with our observation of highest frequency of FM during relaxed wakefulness, which might relate to the difficulty of distinguishing FM from simple fasciculations that may be abundant during wakefulness.

4.1. Strengths and limitations

To our knowledge, this is the largest study on the proportion and time course of FM in sleep lab patients that has been published so far.

The 2007 AASM Scoring Manual for Sleep and Associated Events (Iber et al., 2007), does not refer to sleep stage distribution of EFM or define amplitude criteria for scoring. Early observational studies used 50 μV criteria (Broughton and Tolentino, 1984; Lins et al., 1993), but it was recently suggested that using lower amplitude criteria (i.e. ≥25 μV) might be more sensitive for EFM across all sleep stages (Hoque et al., 2013). This is the first study in a large cohort to confirm that using a lower amplitude criterion of ≥25 μV increases the detection rate of FM and additionally shows a stronger association with arousals, particularly in women, which has not been demonstrated so far (Hoque et al., 2013). Furthermore, FM was more frequent during relaxed wakefulness and REM sleep compared to NREM sleep stages, which has not been previously described and needs to be replicated by other investigators.

There are several limitations to our work. Since our study sample included all patients attending our sleep lab at a certain time-period, other patient groups, particularly RBD and parasomnias, may be underrepresented in this study. Data were acquired from a single centre, and due to the retrospective nature of the study, control data were not collected, which limits generalizability. Furthermore, it has previously been suggested that it is difficult to distinguish FM from benign fasciculations, and that both, FM and fasciculations may represent different expressions of a range of motor phenomena (Montagna et al., 1988). This might have influenced the number of FM events documented in our study sample and may at least partly explain the high frequency of FM during relaxed wakefulness. Furthermore, a more detailed analysis of the temporal relation of arousals with the occurrence of FM should be addressed in future studies. Standard EMG recordings during polysomnography at our centre are limited to mentalis and tibialis anterior muscles. Due to the retrospective nature of the study, no other muscle groups were investigated, which does not allow interpretation of distribution or rostrocaudal propagation of FM. Since nerve conduction studies were not routinely performed in our cohort, a possible association of EFM with abnormal neurophysiological findings cannot be excluded (Raccagni et al., 2016). Lastly, since PSGs were acquired in 2011–2013, sleep was scored according to Rechtschaffen and Kales (1968) and not according to AASM scoring standards (Iber et al., 2007).

5. Conclusion

Our results suggest that FM does not depend on sleep-related breathing disorders, but rather represents a ubiquitous motor phenomenon accentuated during relaxed wakefulness and REM sleep and in older men. In women, FM is less frequently encountered and particularly FMI25 may be a surrogate marker for higher arousal indices.

Acknowledgements

The authors would like to thank all patients who participated in the study as well as Klaus Spiessl and Silvia Eibensteiner for assistance with FM scoring.

Declaration of Competing Interest

The authors have no financial or non-financial conflicts of interest to declare.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

American Academy of Sleep Medicine. International Classification of Sleep Disorders, 2nd ed. (ICSD-2). Westchester, Ill; 2005.
American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed. Diagnostic and Coding Manual. Westchester, Ill; 2014.
American Sleep Disorders Association. Classification of sleep disorders: diagnostic and coding manual. Rochester, Minnesota: American Sleep Disorders Association; 1990.
American Sleep Disorders Association. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173–84.
Amihăesei IC, Mungiu OC. Main neuroendocrine features and therapy in primary sleep troubles. Rev Med Chir Soc Med Nat Iasi 2012;116:862–6.
Auer M, Frauscher B, Hochleitner M, Högl B. Gender-specific differences in access to polysomnography and prevalence of sleep disorders. J Womens Health (Larchmt) 2018;27:525–30.
Broughton R, Tolentino MA. Fragmentary pathological myoclonus in NREM sleep. Electroencephalogr Clin Neurophysiol 1984;57:303–9.
Broughton R, Tolentino MA, Krelina M. Excessive fragmentary myoclonus in NREM sleep: a report of 38 cases. Electroencephalogr Clin Neurophysiol 1985;61:123–33.
Dagnino N, Loeb C, Massazza G, Sacco G. Hypnic physiological myoclonias in man: an EEG-EMG study in normals and neurological patients. Eur Neurol 1969;2:47–58.
Frauscher B, Gabelia D, Mitterling T, Biermayr M, Bregler D, Ehrmann L, et al. Motor events during healthy sleep: a quantitative polysomnographic study. Sleep 2014;37:763–73.
Frauscher B, Kunz A, Brandauer E, Ulmer H, Poewe W, Högl B. Fragmentary myoclonus in sleep revisited: a polysomnographic study in 62 patients. Sleep Med 2011;12:410–5.
Gassel MM, Marchiafava PL, Pompeiano O. Phasic changes in muscular activity during desynchronized sleep in unrestrained cats. An analysis of the pattern and organization of myoclonic twitches. Arch Ital Biol 1964;102:449–70.
Hoque R, McCarty DE, Chesson AL. Manual quantitative assessment of amplitude and sleep stage distribution of excessive fragmentary myoclonus. J Clin Sleep Med 2013;9:39–45.
Iber C, Ancoli-Israel S, Chesson AL, Quan SF, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
Lins O, Castonguay M, Dunham W, Nevsimalova S, Broughton R. Excessive fragmentary myoclonus: time of night and sleep stage distributions. Can J Neurol Sci 1993;20:142–6.
Montagna P, Liguori R, Zucconi M, Sforza E, Lugaresi A, Cirignotta F, et al. Physiological hypnic myoclonus. Electroencephalogr Clin Neurophysiol 1988;70:172–6.
Pothoff RF. Statistical aspects of the problem of biases in psychological Tests. Chapel Hill: University of North Carolina, Department of Statistics: Institute of Statistics Mimeo Series No. 479; 1966.
Raccagni C, Löscher WN, Stefani A, Wanschitz J, Kraemer L, Heidbreder A, et al. Peripheral nerve function in patients with excessive fragmentary myoclonus during sleep. Sleep Med 2016;22:61–4.
Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, Maryland: U.S. National Institute of Neurological Diseases and Blindness, Neurological Information Network; 1968.
Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–7.
Weaver B, Wuensch KL. SPSS and SAS programs for comparing Pearson correlations and OLS regression coefficients. Behav Res Methods 2013;45:880–95.