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Original Article

Fragmentary myoclonus in sleep revisited: A polysomnographic study in 62 patients

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ABSTRACT

Study objectives: To investigate the frequency of fragmentary myoclonus (FM) in a sleep-disorder population, to analyze its distribution across sleep stages and to examine potential associations with clinical correlates and night-to-night variability.
Design: Retrospective review of 102 polysomnographic records.
Setting: Sleep laboratory at a University Hospital Neurology Department.
Patients: Sixty-two sleep-disorder patients.
Interventions: None.
Measurements and results: Fragmentary myoclonus (FM) was counted according to published criteria. Sleep stage specific FM indices (FMI) were calculated for each patient. Median FMI was 39.5/h sleep. FMI was the highest in REM sleep, followed by similar indices in wakefulness, S1 and S2 sleep, and was the lowest in S3/S4 sleep (n.s.). FMI increased with age ($\rho = 0.350$, $P = 0.005$). Men had a higher FMI than women (median 55.8/h vs. 24.1/h, $P = 0.042$). In addition, FMI was positively correlated with the presence of sleep-related breathing disorders ($\rho = 0.270$, $P = 0.036$), respiratory indices (apnea–hypopnea index: $\rho = 0.403$, $P = 0.002$; oxygen desaturation index: $\rho = 0.378$, $P = 0.004$) and body mass index ($\rho = 0.28$, $P = 0.028$). In a linear regression model, age, male sex and oxygen desaturation index were significant ($P < 0.05$). FMI night-to-night variability was 1.6 (range: 1.0–3.9).
Conclusion: Fragmentary myoclonus was present in every patient of this sleep-disorder population. Its clinical significance is unknown, but the association with oxygen desaturation index points to an association with sleep-related breathing disorders. Since FMI was similar during wakefulness and light sleep, these data challenge the concept of a primarily sleep-related phenomenon.

1. Introduction

Broughton and Tolentino introduced the term fragmentary myoclonus of sleep in 1984 for very brief (below 150 ms) potentials in surface electromyography recorded during polysomnography. They described fragmentary myoclonus as resulting in invisible or hardly visible twitches or jerks occurring at irregular intervals in an asymmetrical fashion on both sides of the body [1]. This definition was made based on a case report about a patient with excessive daytime sleepiness who had abnormal amounts of fragmentary myoclonus persisting throughout all stages of non-rapid eye movement (NREM) sleep [1]. In 1985, the same group reported excessive fragmentary myoclonus in 38 patients [2]. They observed that excessive fragmentary myoclonus was associated with various sleep disorders (such as sleep-related breathing disorders, periodic limb movements in sleep, narcolepsy, hypersomnia, sleep fragmentation and insomnia) [2]. Lins et al. introduced a scoring method for the quantification of fragmentary myoclonus: the fragmentary myoclonus index [3].

The clinical relevance of fragmentary myoclonus is unknown. Excessive fragmentary myoclonus was first introduced in the International Classification of Sleep Disorders (ICSD) in 1990 [4a]. According to the current version of the ICSD (ICSD-2) it is classified in the category "Isolated symptoms, apparently normal variants and unresolved issues" [4b]. Excessive fragmentary myoclonus is defined as at least five characteristic fragmentary myoclonus electromyographic potentials per minute during at least 20 min of NREM sleep. A pathological fragmentary myoclonus index for the whole night has not been defined [4b,5].

A detailed analysis of fragmentary myoclonus in a larger patient sample and confirmation of the results obtained by Broughton [1,2] has never been performed.

The aim of the present study is to investigate the frequency of fragmentary myoclonus in a mixed sleep-disorder population, to analyze its distribution across sleep stages, to evaluate effects of gender and age, to study its association with sleep stages and

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clinical correlates, and to examine the night-to-night variability of fragmentary myoclonus within subjects.

2. Methods

2.1. Design

A review of all polysomnographies performed at the sleep laboratory of the Department of Neurology, Innsbruck Medical University between January 1 and December 31, 1997, was carried out. Polysomnographic records were read from magnetic optical disks. All records containing reliable bipolar surface EMG of both tibialis anterior muscles were included. Polysomnographic records that did not include bipolar surface EMG of both tibialis anterior muscles, records with artifacts in the tibialis anterior electromyography, records of bad quality, and records on unreadable storage media were excluded.

2.2. Patient collective

Three hundred fourteen polysomnographic records of 138 patients were reviewed. One hundred and fifty-five records of 76 patients did not include bilateral tibialis anterior electromyographic electrodes due to nasal CPAP titration ($n = 139$), torticollis protocol ($n = 6$), and other protocols ($n = 10$). Fifty-seven recordings were excluded for technical reasons (magnetic optical disks not readable or artifacts in the tibialis anterior electromyography during parts of the recording). For the final analysis, the remaining 102 records of 62 patients with various sleep disorders were included (1 night of polysomnographic recording in 62 patients, 2 nights of consecutive polysomnographic recording in 36 patients, 3 nights of consecutive polysomnographic recording in 3 patients, and 4 nights of consecutive polysomnographic recording in 1 patient). The patients were 13 women and 49 men [median age 51.5 (range 19–75)]. Twenty-four patients (38.7%) had sleep-related breathing disorders, 18 patients (29.0%) had restless legs syndrome/periodic limb movements in sleep index >15/h, 4 (6.5%) primary insomnia, 3 (4.8%) hypersomnia (2 narcolepsy, 1 idiopathic hypersomnia), 3 (4.8%) non-REM parasomnias, 3 (4.8%) REM parasomnias (2 REM sleep behavior disorder, 1 nightmares), and 2 bruxism (3.2%). Sleep disturbances due to neurological comorbidity were present in 8 (12.9%) patients (4 Parkinson disease, 2 traumatic brain injury, 2 cerebral ischemia).

2.3. Polysomnographic recording and electrode placement

Polysomnographic recording was performed using Schwarzer Brainlab® 3.0, Munich, Germany, with data storage on a 1.3 GB magnetic optical disk. The electrodes were placed according to the international 10–20 system [6]. Since polysomnography was performed in 1997 before the new AASM scoring criteria [5] were introduced, electroencephalography consisted of C3-A2 and C4-A1 only, horizontal and vertical electrooculography, mental and submental surface electromyography, and bipolar surface electromyography of both tibialis anterior muscles, as well as one channel electrocardiogram and respiratory recording including oro-nasal airflow by thermocouple, blood oxygen saturation by pulse oximetry, thoracic and abdominal breathing effort by strain gauge and snoring by laryngeal microphone.

The bipolar tibialis anterior surface electromyographic electrodes were placed 4–6 cm apart along the longitudinal axis on the belly of the muscle [7]. The tibialis anterior electromyographic potentials were recorded with low pass filters set at 50 Hz and high pass filters set at 250 Hz. The sampling rate was 500 Hz. Sensitivity was set to 100 μV/cm and adjusted as needed for visual analysis.

2.4. Sleep analysis

For sleep stage scoring, 30-s epochs were visually scored according to the criteria of Rechtschaffen and Kales [8]. Sleep period time was the period of time measured from sleep onset until the final awakening and included the amount of actual sleep time during the time in bed, wakefulness after sleep onset and movement time. The apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The oxygen desaturation index (ODI) was defined as the number of drops in oxygen saturation of 4% or more from baseline per hour of sleep.

2.5. Fragmentary myoclonus analysis

Fragmentary myoclonus was defined according to the clinical description given by Broughton et al. [1] and modified by Lins et al. [3] as muscle surface potentials of the tibialis anterior muscle with an amplitude of 50–200 μV and a duration of less than 150 ms. [1,3]. One of the authors (AK) visually counted fragmentary myoclonus. To count fragmentary myoclonus on the screen, the digital EEG ruler provided by the polysomnographic software (Schwarzer Brainlab®) which included amplification by 4 times was used. A senior neurologist with specialization in sleep medicine (BH) carefully supervised all counting. To quantify fragmentary myoclonus, the fragmentary myoclonus index as defined by Lins et al. [3] was calculated. Each 30-s scoring epoch was divided into ten 3-s mini epochs. The number of these mini epochs with at least one fragmentary myoclonus potential fulfilling the criteria was counted for each 30-s epoch, resulting in a number between 0 and 10 (Fig. 1). Fragmentary myoclonus indices were calculated for each sleep stage as the total amount of fragmentary myocloni per sleep stage divided by hour of each sleep stage. Phasic muscle activity of REM-sleep [9,10] which fulfilled the criteria for fragmentary myoclonus [3,5] was counted as FM.

2.6. Statistics

SPSS® for Macintosh version 16.0 was used for data analysis. Data were checked for normal distribution using the 1-sample Kolmogorov–Smirnov test. Since normality assumption was not fulfilled, variables were presented as medians (range) or frequencies (percentages), as applicable. Gender differences were investigated by applying the two-tailed Mann–Whitney *U*-test. The overall effect of sleep stage on fragmentary myoclonus indices/h were analyzed by Friedman's test. To assess bivariate and multivariate correlations of quantitative sleep variables with the fragmentary myoclonus index, Pearson correlation coefficients and linear regression analysis were used on natural log-transformed variables. All variables that reached significance in bivariate testing were used as predictors of fragmentary myoclonus indices in the linear regression model.

In addition, in order to examine the night-to-night variability, we compared the overall fragmentary myoclonus index of the first night with the following nights in all patients who had undergone at least two polysomnographies ($n = 36$). For each patient, we divided the overall fragmentary myoclonus index of the night with the highest rate by the night with the lowest rate.

In addition, we calculated percentiles to establish the range of fragmentary myoclonus indices which were reached by 95% of investigated subjects. A *P*-value of less than 0.05 was considered significant.

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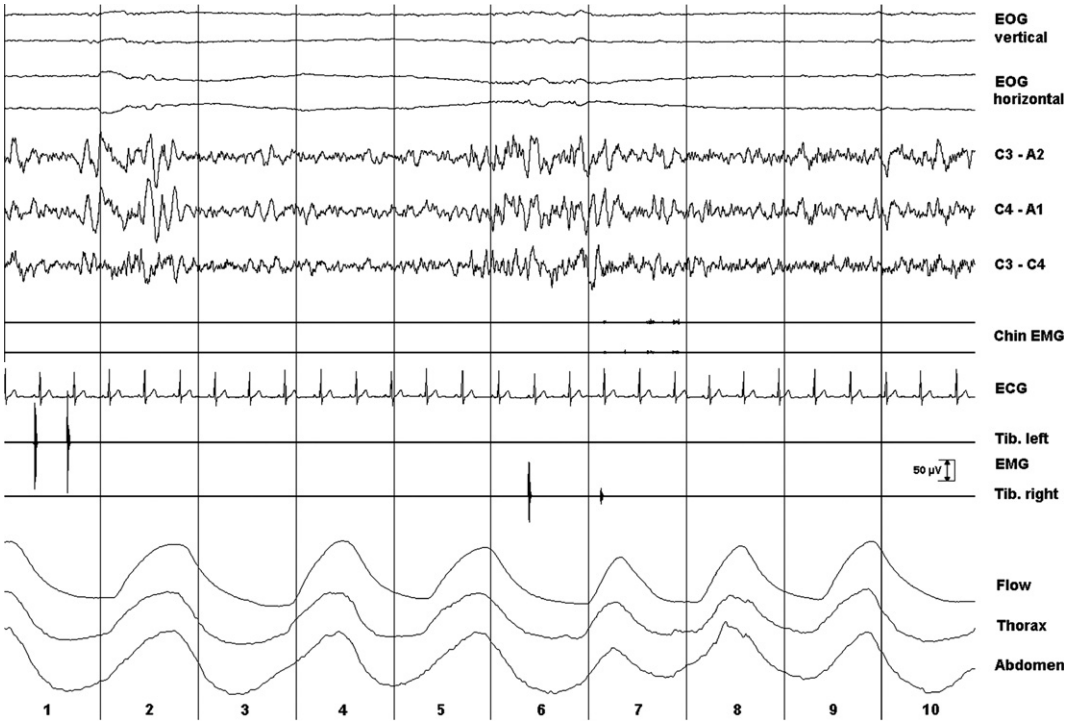

Fig. 1. Thirty-second stage 2 epoch divided into ten 3-second mini epochs with fragmentary myoclonus on the tibialis anterior EMG. The potential of mini epoch 7 does not exceed 50 µV and was therefore not counted. Mini epochs 1 and 6 each contain at least one potential exceeding 50 µV of less than 150 ms in duration which satisfies the criteria for fragmentary myoclonus. Mini epoch 1 contains 2 potentials which are counted as one mini epoch containing fragmentary myocloni according to the criteria.

3. Results

3.1. Frequency and sleep stage distribution

Every subject in this study had fragmentary myoclonus. The median fragmentary myoclonus index was 39.5/h, ranging from 4.0 to 370.9. The fragmentary myoclonus indices of all patients are shown in Fig. 2.

We found that the fragmentary myoclonus index was highest during REM sleep [median 55.0 (0–397.0)], followed by similar indices during wakefulness [median 43.3 (1.7–709.1)], S1 sleep [median 45.4 (2.5–380.5)], and S2 sleep [median 47.8 (1.4–433.6)], and was lowest in S3/S4 sleep [median 31.9 (0–320)]. The overall difference between sleep stages was significant ($P < 0.001$); however, the difference did not withstand post hoc pairwise testing with Bonferroni correction for multiple comparisons. This is illustrated in Fig. 3.

3.2. Sex differences

The fragmentary myoclonus indices of 49 men and 13 women were compared. Men had a median fragmentary myoclonus index of 55.8 (4.0–370.9), and women a median fragmentary myoclonus index of 24.1 (6.7–250.6). The difference was statistically significant ($P = 0.042$).

3.3. Age effects

The fragmentary myoclonus index increased with age. A moderate but highly significant correlation of the fragmentary myoclonus index and age was found (Spearman's $\rho = 0.350$, $P = 0.005$; see Fig. 4).

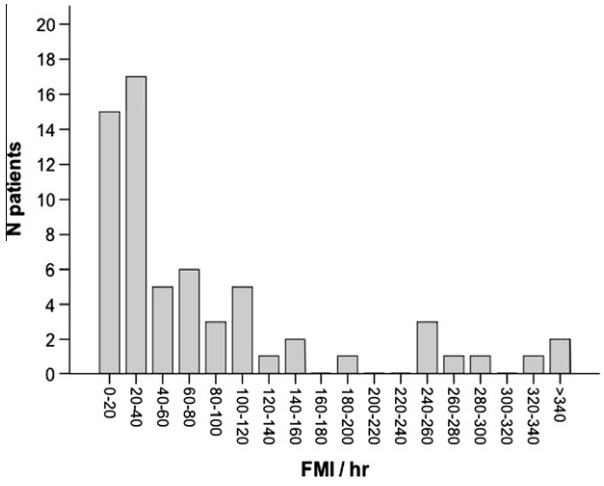

Fig. 2. Bar chart showing the distribution of the fragmentary myoclonus indices (FMI) among patients. The *x*-axis represents the FMI and the *y*-axis the number of patients. Note that most patients had low FMI, whereas high FMI was only present in few patients.

3.4. Association with body mass index

There was a positive correlation between fragmentary myoclonus index and body mass index (Pearson's $\rho = 0.302$, $P = 0.02$).

3.5. Association with sleep disorders

Patients with sleep-related breathing disorders had significantly higher fragmentary myoclonus indices than patients without sleep-related breathing disorders [SRBD vs. no SRBD, 74.4 (8.2–370.9) vs. 37.4 (4.0–288.6); $P = 0.036$]. In addition, the

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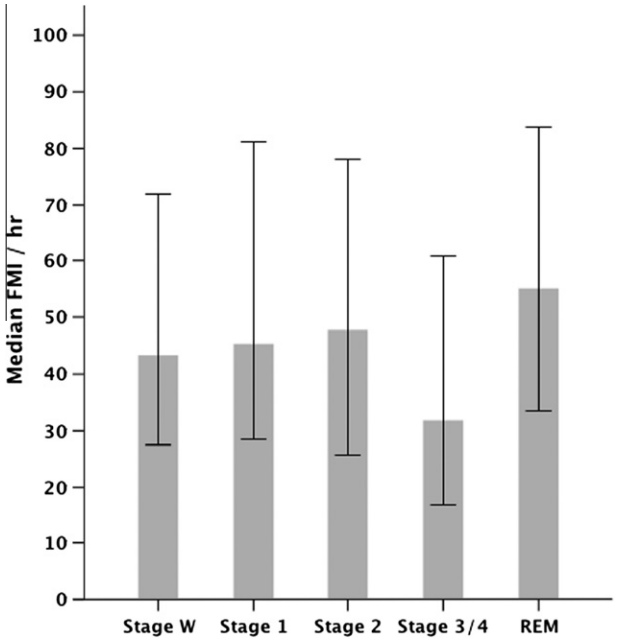

Fig. 3. Median distribution of the fragmentary myoclonus indices (FMI) across wakefulness and different sleep stages. Whiskers represent the 95% confidence intervals of the median.

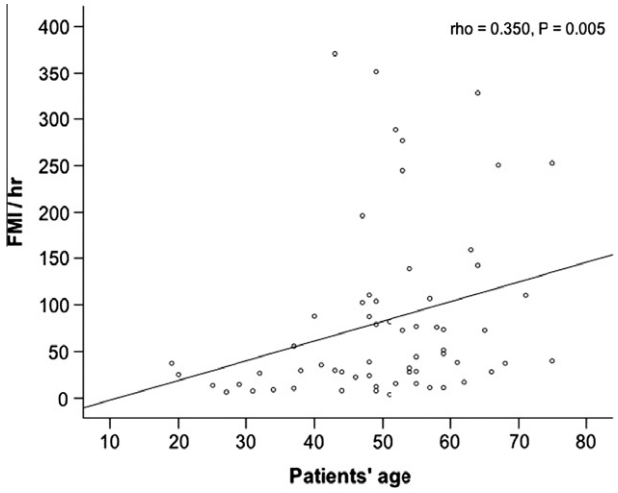

Fig. 4. Correlation of age given on the *x*-axis and the frequency of fragmentary myocloni per hour sleep (FMI) on the *y*-axis (Spearman's $\rho = 0.350$; $P = 0.005$).

fragmentary myoclonus index increased with the apnea–hypopnea index (Pearson's $\rho = 0.403$, $P = 0.002$) and with the oxygen desaturation index (Pearson's $\rho = 0.378$, $P = 0.004$). Correlations are illustrated in Fig. 5. In spite of this, significant associations between the fragmentary myoclonus index and major categories of sleep disorders were not found (see Table 1).

3.6. Multivariate analysis

All variables reaching significance in bivariate testing (sex, age, body mass index, presence of sleep-related breathing disorders, apnea–hypopnea index, oxygen desaturation index) were used as predictors for fragmentary myoclonus rates in a linear regression model. Multivariate analysis revealed a significant association between the fragmentary myoclonus index, age (standardized coefficient = 0.370, $P = 0.005$), male gender (standardized

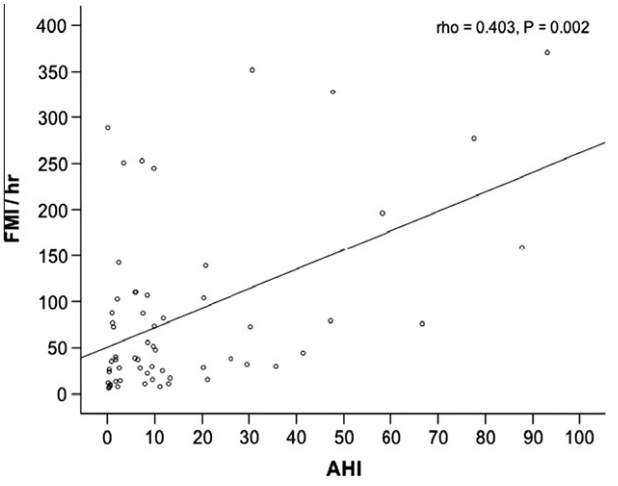

Fig. 5a. Correlation of the frequency of fragmentary myocloni per hour sleep (FMI) given on the *x*-axis and the apnea–hypopnea index (AHI) on the *y*-axis (Pearson's $\rho = 0.403$; $P = 0.002$).

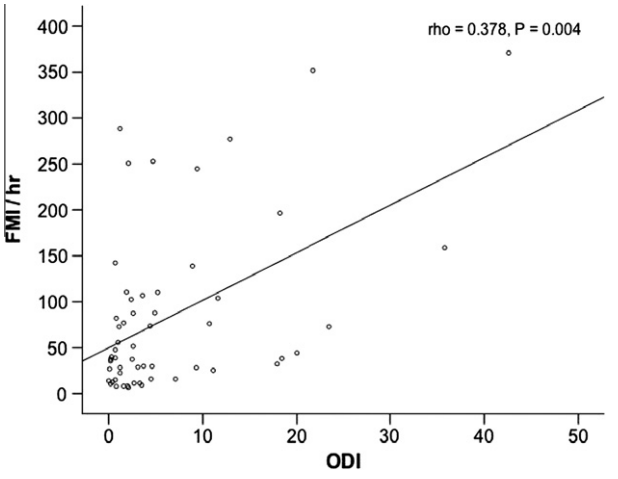

Fig. 5b. Correlation of the frequency of fragmentary myocloni per hour sleep (FMI) given on the *x*-axis and the oxygen distress index (ODI) on the *y*-axis (Spearman's $\rho = 0.378$; $P = 0.004$).

coefficient = 0.271, $P = 0.032$) and oxygen desaturation index (standardized coefficient = 0.251, $P = 0.049$). The body mass index, presence of sleep-related breathing disorders, as well as apnea–hypopnea index did not reach statistical significance in the linear regression model.

3.7. Night-to-night variability within subjects

Thirty-six patients were studied during at least two consecutive nights. Fragmentary myoclonus index night-to-night variability was 1.6 (range 1.0–3.9).

3.8. Quantitative confirmation of a cut-off for excessive fragmentary myoclonus

Ninety-five percent of investigated subjects had a fragmentary myoclonus index between 4.0 and 321.9/h.

4. Discussion

Every patient in this mixed sleep-disorder population exhibited fragmentary myoclonus. Median fragmentary myoclonus index

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Table 1
Association of fragmentary myoclonus indices (FMI) with main sleep diagnoses.

	SRBD	RLS/PLMS > 15	Hypersomnia	Primary insomnia
Number of patients	24 (23 m, 1 w)	18 (12 m, 6 w)	3 (1 m, 2 w)	4 (2 m, 2 f)
Age of patients	52.8 ± 7.4	57.2 ± 10.5	41.7 ± 22.0	43.5 ± 13.2
Median FMI/h	**74.4**	**58.1**	**7.8**	**13.7**
Range	**8.2–370.9**	**8.2–370.9**	**6.7–250.6**	**10.6–51.6**
P-value	**0.036**	**0.132**	**0.309**	**0.090**

SRBD, sleep-related breathing disorder; RLS, restless legs syndrome; PLMD, periodic limb movement disorder; m, men; w, women.

was 39.5/h, ranging from 4.0 to 370.9. Fragmentary myoclonus index was higher in men than in women and related to age and oxygen desaturation index. This study confirms and extends previous studies on fragmentary myoclonus.

Previous studies have also found significantly more fragmentary myoclonus in men than in women [2,3]. In our study, this gender difference was not due to age, since men and women were of similar age. However, because sleep-related breathing disorders were present in 23 out of 49 men, but only 1 out of 13 women, we cannot rule out that the gender difference in fragmentary myoclonus was influenced by sleep-related breathing disorders. Nevertheless, gender withstood multivariate testing.

The fragmentary myoclonus index was moderately correlated with the oxygen desaturation index. This may point to an association with sleep breathing disorders, as previously suggested by Broughton [2]. We consider the lack of an association between fragmentary myoclonus and sleep-related breathing disorders as a category in the multivariate model as not being in contrast with this significant finding because the diagnosis of sleep-related breathing disorder was only made on a categorical basis (present or absent), but not subdivided for severity. Equally, we failed to demonstrate an association with restless legs syndrome or a periodic leg movement in sleep index above 15/h.

The activity of fragmentary myoclonus was highest in REM sleep and decreased from light to deep sleep stages. Therefore, the generator of this phasic muscle activity seems to be influenced by sleep. The fact that fragmentary myoclonus is most frequent in REM sleep is not surprising because phasic muscle activity is also a property of normal REM sleep. A similar relationship of fragmentary myoclonus indices with sleep stage was also found in a previous study [3], which did not include fragmentary myoclonus counts during wakefulness. Montagna et al. investigated a similar phenomenon termed hypnic myoclonus (duration below 100 ms, amplitude not considered) in seven healthy male subjects. They found a similar sleep stage distribution to our study [11].

Fragmentary myoclonus is observed during routine polysomnography. Our data, however, show that fragmentary myoclonus is not restricted to sleep, but is also present during relaxed wakefulness [11]. Therefore, one might consider that fragmentary myoclonus is present during sleep and wakefulness. Besides relaxed wakefulness, fragmentary myoclonus is usually masked by physiological motor activity during wakefulness. Based on our data and those of Montagna [11], the concept of fragmentary myoclonus as primarily sleep-related phenomenon can be questioned.

The pathophysiology and clinical substrate of fragmentary myoclonus remains obscure. Vertrugno hypothesized that fragmentary myoclonus originates in the brainstem [12]. The inverse relation of fragmentary myoclonus index with sleep depth and the high frequency in REM sleep could be in line with this hypothesis. On the other hand, a peripheral genesis of at least a substantial proportion of fragmentary myoclonus activity cannot be ruled out. We suggest that at least a proportion of fragmentary myoclonus might relate to spontaneous single motor neuron discharges, but this remains to be investigated in further studies.

The presence of fragmentary myoclonus in every single subject of our study may indicate that it is a normal phenomenon. But the fragmentary myoclonus index was low in many patients and high in a few. Possibly, only excessive fragmentary myoclonus is pathological, as has been previously suggested by Broughton [2]. Broughton and colleagues provided an arbitrary cut-off for the diagnosis of excessive fragmentary myoclonus of five fragmentary myocloni potentials per minutes over a duration of 20 min. This arbitrary cut-off was introduced in the ICSD-2/AASM criteria [4b,5] and is since then mandatory for a diagnosis of excessive fragmentary myoclonus. To estimate the potential range of normality of fragmentary myoclonus, we calculated the range of fragmentary myoclonus indices, which were reached by 95% of investigated subjects. This range was between 4.0 and 321.9/h. But it must be kept in mind that our data were obtained from patients belonging to a mixed sleep-disorder population and not from healthy controls, who would have represented real-life circumstances in the setting of routine polysomnographic testing.

One final caveat must be made. We cannot definitively exclude that some of the electromyographic potentials we counted as fragmentary myoclonus correspond to artifacts. Nevertheless, the clear relationship with sleep stages and age, as well as the only moderate night-to-night variability of fragmentary myoclonus within subjects are strong arguments against the assumption that a major proportion of potentials counted were artifacts.

In summary, fragmentary myoclonus is ubiquitous in a mixed sleep-disorder population, suggesting that it is a physiological phenomeon. The clinical significance of fragmentary myoclonus is unknown, but its association with oxygen desaturation index points to an association with sleep-related breathing disorders. Since the fragmentary myoclonus index was of similar intensity during both wakefulness and light sleep, our data challenge the concept of an isolated sleep-related phenomenon.

Conflicts of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2010.08.016.

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