SOREM and CAP Parameters in Narcolepsy Patients and Healthy Subjects

Huyen Nhung Hoang, Quoc Khai Le, and Quang Linh Huynh

Abstract This study aimed to compare sleep architects and CAP parameters between patients with Narcolepsy and the normal person using the electroencephalogram signal (EEG) analysis. In this study, we analyzed sleep data from five Narcolepsy patients and fourteen normal controls. Participants' macrostructure parameters and CAP parameters were calculated and compared to indicate the abnormal in narcoleptics' nocturnal sleep. A prime abnormal in Narcolepsy patient's sleep structures was the early onset of REM with significant shot REM latency; this phenomenon was observed in two out of five patients' hypnograms. The nocturnal sleep of Narcolepsy patients was usually disturbed by sleep arousals that appeared regularly at night, which reduced the quality of nocturnal slumber. In this study, Narcolepsy individuals had a lower CAP/NREM rate, shorter CAP total time, and a decreased in the A1 index during NREM sleep compared to healthy individuals. The obtained results suggested that people with Narcolepsy be likely to have a short REM latency with fragmented night sleep that reduced sleep quality. The increase in the CAP ratio could relate to the instability of night sleep in Narcolepsy patients. A further study on EEG wave activity should be conducted to assist the inequality between a group of Narcolepsy patients and another group of normal subjects.

Keywords Narcolepsy · CAP · Hypnogram · EEG · Electroencephalogram

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1 Introduction

Narcolepsy is unknown by the majority of the population in the world as it is a rare sleep disorder that is primarily characterized by four symptoms, including excessive daytime sleepiness (EDS), cataplexy, disturbed nocturnal slumber, and hallucinations [1]. There are two types of hallucinations that a Narcolepsy individual may face that happens when a person is waking up and when the person is falling asleep, call hypnopompic hallucinations and hypnagogic hallucinations [1]. Several articles report that Narcolepsy might occur for the first time at any time from an early age to under 50 years old [2]. Some research indicates around the age of 15 and the age of 36 as two peak time periods of narcolepsy onset [2]. In the United States, the disorder has been estimated to affect 0.05 percent of the population, affecting both males and females equally [1]. The prevalence seems to be higher or lower in some regions. For instance, Narcolepsy is commonest in the Japanese population, which affects at a rate of 160 cases per 100,000 individuals, but the percentage of Narcolepsy is lower in the Jewish and Saudi Arabian population, only 10 cases for every 100,000 persons [1]. However, determining its true frequency in the general population over the world with some difficulties since it takes years to be recognized and diagnosed.

In 1880, Gelineau first described Narcolepsy disorder in the medical literature. At an early age, Narcolepsy was diagnosed according to four main symptoms: excessive daytime sleepiness, sudden loss of muscular tonus, fragmented slumber, and vivid hallucinations [3]. Years later, the presence of sleep-onset rapid eye movement (SOREM) in narcolepsy sleep stages had been found as a shred of abnormal evidence for diagnosing by Vogel, and Honda et al. [4], had correlated the disease with the lack of Class II HLA-DR2 antigens in patients' spinal fluid in 1983 [4]. Many studies were conducted to find the relation between cerebrospinal fluid (CSF) hypocretin levels and Narcolepsy during the last decade. These studies indicate that 90% of the patients with Narcolepsy have lower hypocretin levels than in healthy individuals, which contributes to the evidence that Narcolepsy is an autoimmune disorder [5, 6].

Diagnosing Narcolepsy requires several tests, including polysomnography (PSG), Multiple Sleep Latency Test (MSLT). In sleep analysis, polysomnography (PSG) plays an important role as this is a non-invasive technique that makes it possible to collect data from eight hours of night sleep. Previous PSG studies on Narcoleptics mainly focus on sleep architectures, which refer to the basic structural organization of normal sleep. However, misdiagnosis is common in Narcolepsy since the symptoms are unclear; the low awareness of people about this disorder and the features extracted from these studies are not clear enough to diagnose the disorder. In this study, the main purpose is to find the differences in macrostructure and microstructure between Narcolepsy individuals and normal individuals using sleep data.

2 Methodology

This research applies the Declaration of Helsinki principles in human studies.

Macrostructure and microstructure are two major elements of sleep that are defined according to specific events of the EEG signals. For the macrostructure, the whole recording is divided into 30 s epochs then classified into rapid eye movement (REM) or non-REM (NREM) [7]. The microstructure is scored in 1 s epoch based on the transient and phases event in brain electrical activity. Terzano et al. [8] defined a way to analyze the microstructure through the cyclic alternating pattern (CAP). Analyzing the CAP in EEG activity is considered as a method to study sleep instability and sleep disturbance. The CAP includes transient periods (A-phase) that happen in NREM and interrupts the background activities of NREM sleep (B-phase) [8]. The duration of both phases is at least 2 s and no longer than 60 s. A succession of an A-phase and a B-phase form a CAP cycle. A CAP sequence consists of two or more CAP cycles [8, 9]. There are three sub-phases of A-phase (A1, A2, and A3) [8, 9] that can be examined for detailed sleep disturbance analysis or sleep instability.

In this work, we use 14 healthy individuals (31.64 ± 5.20 years) full-night recordings and 5 Narcolepsy patients (31.60 ± 10.33 years) recordings that are uploaded by the Sleep Disorders Center in Parma [8, 10]. The CAP sleep database was downloaded freely from the URL "http://physionet.org/physiobank/database/nstdb/". The database provides the EEG, ECG, EMG waveforms recorded throughout the night stored in .edf files. The scoring of sleep stages and the CAP were detected in agreement with Terzano's reference atlas of rules by expert neurologists trained at the Sleep Center. The scores for each recording are provided as.txt files. This information would be used to calculate the macro and micro sleep parameters of each subject.

2.1 Marco-Structure Parameters

Sleep architecture represents the cyclical sleep pattern when it shifts between sleep stages and provides a picture of what our sleep looks like over the night. Non-rapid eye movement (NREM) and rapid eye movement (REM) sleep are two major parts of sleep architecture. Sleep was usually staged base on the rules of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events. The criteria that were focused on in this study were the duration of each sleep stage in sleep architecture [11]. Normally, sleep goes through NREM stages (N1, N2, N3) before getting into the REM stage. The first cycle often lasts from 90 to 120 min [12]. However, REM sleep does not last for the whole night; in fact, individual sleep architect includes 3–4 cycles between stages of NREM and REM [12]. NREM sleep constitutes most of the total time spent in sleep [12]. REM accounts for around one-fourth of slumber time [12]. Study the sleep architect could reveal sleep quality and other sleep disorders. In narcolepsy studying, the patient's

condition was analyzed based on the symptoms, which made the patient fall asleep unpredictably [1]. Hypnogram visualized the alternating between sleep stages and was normally used to make a quick diagnose of sleep disorders [1].

Sleep architect's criteria were used to evaluate the differences between narcolepsy patients and normal controls. One of the most remarkable differences that distinguish Narcolepsy patients against healthy individuals is the significant short REM sleep latency [13]. Quinnell [14] conducted research to estimate the REM sleep latency in Narcolepsy patients compared to normal controls. The numbers indicated that the onset of sleep in 80% of Narcolepsy patients was around 8 min, followed by REM sleep occurred almost immediately within several seconds [14].

In this study, we focused on the duration of each sleep stage scored in hypnogram and the proportion of each stage to sleep period time. The quality of sleep was estimated through the total sleep period time, total actual sleep time, and the total time of arousals after sleep onset [11]. Figure 1 illustrates the time parameters that were calculated in this study. The hypnogram for each subject was built based on the annotations of sleep stages in the data. Time in bed was defined as the total recording time. The period time between the first time of falling asleep and the last time of waking up was called sleep period time and total actual sleep time was the sleep period time excluded all wakefulness time during the whole night. We calculated the duration time of each type of sleep stage and their percentage. The number of arousal per hour was calculated to estimate the fragmentation of narcolepsy sleep. After calculating all the macrostructure indices, the results were presented in Table 1 as median and standard deviation.

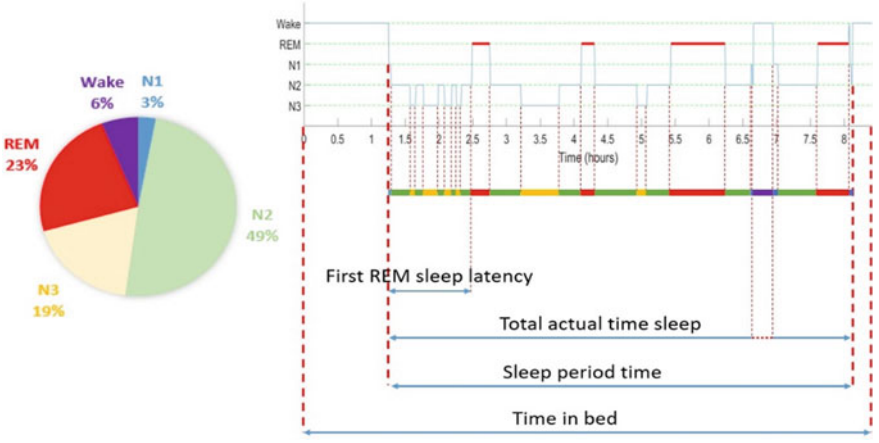

Fig. 1 Example of hypnogram, time and percentage parameters of sleep

Table 1 Comparison of sleep Macrostructural parameters between Narcolepsy group and Controls group (*p-value < 0.05)

	Narcolepsy	Controls	p-value
	Mean ± SD	Mean ± SD	
Sleep period time (min)	451.40 ± 102.80	481.40 ± 14.91	0.105
Total real sleep time (min)	431.10 ± 97.76	479.70 ± 14.16	0.853
N1 time (min)	30.10 ± 23.60	9.80 ± 7.61	0.246
N2 time (min)	170.80 ± 71.01	224.40 ± 20.74	0.165
N3 time (min)	104.40 ± 42.13	121.40 ± 16.46	0.405
REM time (min)	125.80 ± 39.74	124.10 ± 16.65	0.459
Wake time (min)	20.30 ± 7.22	1.70 ± 1.83	**0.033***
Percent of Wakefulness (%)	4.49 ± 1.12	0.35 ± 0.37	**0.042***
Percent of N1 stage (%)	6.58 ± 5.11	2.01 ± 1.50	0.267
Percent of N2 stage (%)	37.39 ± 11.04	46.65 ± 4.50	0.096
Percent of N3 stage (%)	22.43 ± 5.86	25.21 ± 3.14	0.116
Percent of REM stage (%)	29.10 ± 9.22	25.78 ± 3.42	0.869
REM latency (min)	26.00 ± 28.45	74.70 ± 11.01	**0.003***
REM/NREM	0.47 ± 0.21	0.35 ± 0.06	0.229
Awakening (arousals/h)	0.90 ± 0.15	0.15 ± 0.14	0.052

2.2 Micro-structure Parameters

In recent years, slumber instability has been analyzed through CAP parameters since the CAP distribution in NREM stages were considered to have a close relationship with sleep structure. According to Terzano et al. [8], phase A could be classified into three sub-phases (A1, A2, A3). The dominance of A1 subtypes in the N1 stage can be the expression of REM-off activity, while the REM-on activity is reflected by the increase in A2 and A3 subtypes in N2 and N3 [8, 12]. It is reported that in normal sleepers, CAP cycles occurred between 233 to 343 times during sleep [8]. The length of CAP cycles ranges between 25 and 31 s, with a high rate of B-phase [8]. Bruni et al. [12], the mean amount of CAP cycles in children aged between 6 and 10 years old is higher at 363. In children's sleep, the CAP usually lasts longer (30, 49 s) and B-phase consists of 81% of the total CAP time [8]. In this study, we calculated the following: total CAP time, CAP and three subtypes rate, the number of three subtypes and their duration according to Terzano rules [8]. The.txt files provided the

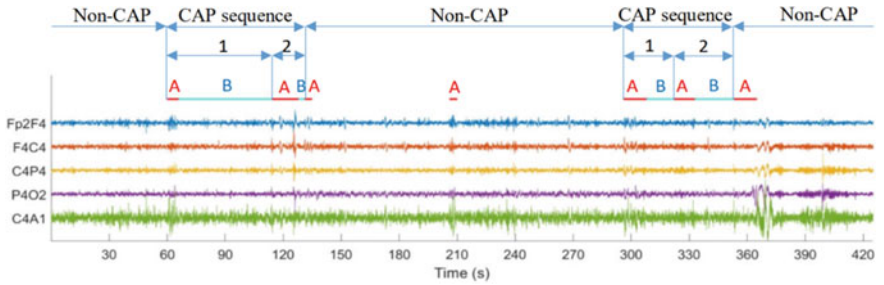

Fig. 2 Minimal requirements for the definition of a CAP sequence. The A phases are marked by red line and the B phases are marked by cyan line. The third A phase of each CAP sequence is not included in that CAP sequence

annotation of A phases and their subtypes. B phases are defined as periods between two A phases; any B phase that lasts longer than 60 s would be excluded. An A phase followed with a B phase form up a CAP cycle. Two or more CAP cycles make up a CAP sequence. Figure 2 provides an example for CAP sequences with at least 2 CAP cycles (numbered as 1, 2); the third A phase belongs to the non-CAP sequence and would be excluded when calculating the microstructure parameters. An isolated A phase, which is separated from other phases by more than 60 s is classified as non-CAP. CAP time (min) is the total time of NREM sleep occupied by CAP sequences and the CAP rate is the fraction of CAP time sleep during the total NREM sleep.

Statistical analysis

All comparisons between groups were carried out using the nonparametric Mann–Whitney test for independent data sets. Differences were considered significant when they reached a $p < 0.05$ level.

3 Results and Discussion

3.1 Macrostructural Variables

Vaňková et al. [15] conducted a research on sleep architects between two groups in order to compare and evaluate the differences that could easily be observed through sleep hypnogram. The researchers indicated that although the total time of sleep between two groups was nearly the same (425.9 ± 75.5 min) for Narcolepsy group and 419 ± 54.5 (min) for the healthy group) [15], the slumber latency was significantly shorter in comparison with the healthy group [15, 16]. In some cases, the onset of REM sleep appeared as soon as the patient falling asleep [15, 16], while in a normal person, REM onset appeared around 80 min after sleep [1].

The results were presented in Table 1. This study observed remarkable differences between the two groups, including early REM onset, wake time, and percentage of wake time. There were some slight differences found for the percentage of the N2 stage and the number of arousals per hour of sleep during nocturnal sleep. Other parameters such as sleep period time, total real sleep time, duration of sleep stages, percentage of REM and NREM's stages were not significantly different between the two groups. Narcoleptic patients often experience disturbed sleep, which expanded the wakefulness and light sleep duration (N1) while reduced deep sleep duration (N2 + N3) for bad sleep. Vivid dreams were one of the prime features in the nocturnal sleep of narcolepsy patients, which might relate to the early appearance of the REM stage in hypnogram. There are searches indicate some similar abnormalities in narcolepsy nocturnal sleep, such as reduced REM and NREM latency, increased micro-arousal in sleep, increased sleep–wake transition, and increased NREM first stage [17–19].

3.2 Microstructural Variables

Terzano et al. [16] reported that the CAP rate might reflect poor slumber quality or sleep disturbed by internal or external factors. Therefore, the CAP rate became one of the criteria for studying sleep disorders [16]. CAP criteria of narcoleptics and normal subjects are presented in Table 2. The result was presented as mean ± standard deviation (SD). In particular, there was no significant difference in the CAP rate in the Narcolepsy group. There were slight differences in the A1 rate and the total number of A3 between the two groups. The A1 rate in the Narcolepsy group was two-thirds of that in the healthy group ($p = 0.052$). In contrast, the total number of A3 in Narcolepsy individuals doubled the number of A3 in healthy individuals ($p = 0.052$). For other criteria, no remarkable differences were observed. Accordingly, phase A3-related indices were better than the CAP rate to distinguish normal sleep from the narcolepsy sleep.

The most well-known microstructure parameters index is CAP, as a higher CAP rate could reflect poor quality sleep [11]. The relationship between CAP sequences and arousals is that the subtypes A2 and A3 correlated positively with arousals, even though there is no statistically significant correlation between subtype A1 and arousals. Parrino et al. [20] indicated that the A1 subtypes dominate during deep NREM sleep and reflect neural mechanisms for maintaining NREM sleep. In contrast, A2 and A3 subtypes are the expressions of NREM disruption. Figure 3 shows the distribution of three sub-phases (A2 and A3 are presented as one bar because they both reflect the disruption of NREM sleep) marked on the sleep hypnogram.

Table 2 Comparison of Microstructural parameters between Narcolepsy group and Controls group (*p < 0.05)

	Narcolepsy	Controls	p-value
	Mean ± SD	Mean ± SD	
CAP time (min)	161.26 ± 83.98	140.17 ± 40.65	0.711
CAP rate (%)	52.73 ± 18.52	40.94 ± 9.64	0.079
Total number of A1	185.60 ± 109.36	192.21 ± 79.95	0.926
Total A1 rate (%)	49.21 ± 9.78	64.47 ± 13.25	0.052
Total number of A2	83.20 ± 58.03	56.57 ± 29.16	0.643
Total A2 rate (%)	17.27 ± 6.97	18.71 ± 7.85	0.781
Total number of A3	135.20 ± 74.35	67.40 ± 22.92	0.052
Total A3 rate (%)	33.52 ± 12.69	16.83 ± 7.26	**0.026***
A mean duration (s)	8.60 ± 1.02	7.79 ± 1.08	0.139
A total duration (min)	62.36 ± 30.94	50.75 ± 16.48	0.517

4 Conclusion

This study has some restrictions. First, there were only 19 recordings used (with only five samples for Narcolepsy groups) in this study and the samples were not matched by age and sex factors. The sample included in this study were from two different groups of people without age-match or gender-match, which could lead to limitations of the study results. Second, although there are significant differences in SOREM and A3 index, these features are not strong enough to recognize or diagnose every individual. In conclusion, the narcoleptic patients investigated in the study show early REM stage sleep. Compared to controls, there was a slight increase in CAP rate in narcolepsy patients which related to poor sleep quality. There were studies that showed contrary results [3, 13, 15]; in our study, some samples show a lower CAP rate but not for all the cases. However, the sample size is limited, and the p-value does not show a remarkable difference between the two groups. For better performance, it is needed to add more samples for patient group as well as match the samples by age and sex. Our study shows some noticeable features in narcolepsy patients that are different from normal individuals which may help detect the disorder. Other woths could be conducted to improve the diagnosing method, such as analyzing power spectrum of the EEG wave forms.

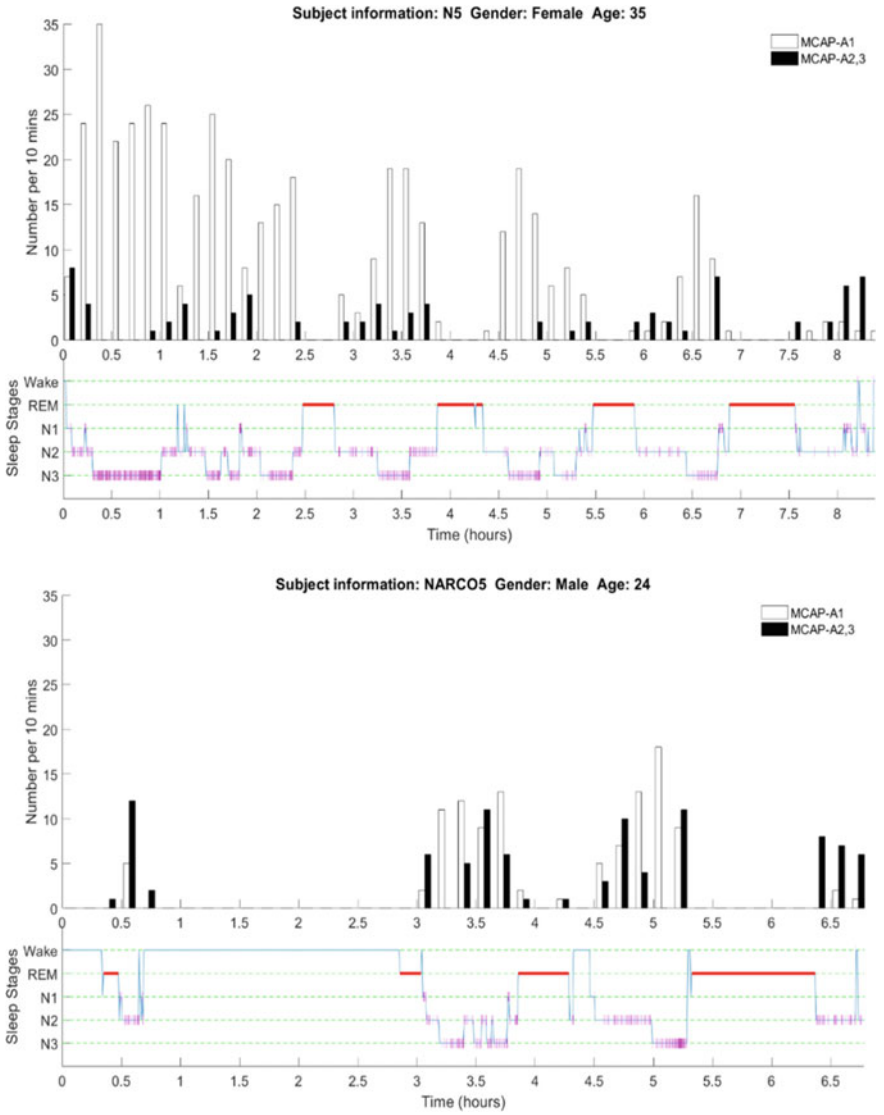

Fig. 3 Distribution of three sub-phases (white bars represent A1, black bars represent A2 and A3) marked on the sleep hypnogram. Each bar illustrated the number of events happen every 10 min over the recording night. The top panel indicated the hypnogram and the number of phase A in normal persons compared with the hypnogram and the number of phase A in a narcolepsy patient (bottom panel). Small magenta vertical lines on the hypnogram indicated the occurrence of each sub-phase event. Thick red lines represented the appearance and endurance of REM sleep stage. Sleep onset REM periods (SOREMs) in narcoleptic patient appeared very early (almost as soon as the patient fall asleep), while in a healthy individual subject SOREM appeared 2.5 h after the subject falling asleep. A significant difference can be observed through the graphs were the reduction in the number of phase A1 and the increase in the number of phase A2 and phase A3 in narcoleptic individual compared to healthy control

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Conflicts of Interest The authors declare no conflict of interest.

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