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Sleep–wake patterns, non–rapid eye movement, and rapid eye movement sleep cycles in teenage narcolepsy

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ABSTRACT

Background: To further characterize sleep disorders associated with narcolepsy, we assessed the sleep–wake patterns, rapid eye movement (REM), and non-REM (NREM) sleep cycles in Chinese teenagers with narcolepsy.

Methods: A total of 14 Chinese type 1 narcoleptic patients (13.4 ± 2.6 years of age) and 14 healthy age- and sex-matched control subjects (13.6 ± 1.8 years of age) were recruited. Ambulatory 24-hour polysomnography was recorded for 2 days, with test subjects adapting to the instruments on day 1 and the study data collection performed on day 2.

Results: Compared with the controls, the narcoleptic patients showed a 1.5-fold increase in total sleep time over 24 hours, characterized by enhanced slow-wave sleep and REM sleep. Frequent sleep–wake transitions were identified in nocturnal sleep with all sleep stages switching to wakefulness, with more awakenings and time spent in wakefulness after sleep onset. Despite eight cases of narcolepsy with sleep onset REM periods at night, the mean duration of NREM–REM sleep cycle episode and the ratio of REM/NREM sleep between patients and controls were not significantly different.

Conclusion: Our study identified hypersomnia in teenage narcolepsy despite excessive daytime sleepiness. Sleep fragmentation extended to all sleep stages, indicating impaired sleep–wake cycles and instability of sleep stages. The limited effects on NREM–REM sleep cycles suggest the relative conservation of ultradian regulation of sleep.

1. Introduction

Narcolepsy typically occurs during adolescence and persists into adult life [1,2]. It is a severe sleep disorder resulting from selective loss of hypocretin (Hcrt, also called orexin) in the lateral hypothalamic area [3–6], with well-defined clinical features including excessive daytime sleepiness (EDS) and nocturnal sleep disorders, with or without cataplexy [7–9]. Narcolepsy patients often have severe sleepiness, which makes it a struggle to remain awake during daytime. Nocturnal sleep disorder is characterized by frequent sleep interruptions and longer awake time, which is also called fragmented sleep. Other symptoms such as obesity [7,10], poor health-related quality of life [11], and obstructive sleep apnea syndrome [12] are also common in narcolepsy patients.

As an important neuromodulator in the brain, Hcrt strongly mediates sleep–wake cycles and regulates the inherent sleep architecture. Typically, the sleep pattern in narcolepsy is characterized by a polyphasic distribution over 24 hours [13,4] and frequent rapid eye movement (REM) sleep onset [15]. However, the quality of sleep–wake cycles/patterns in narcolepsy is somewhat inconclusive. One view is that the patients compensate for their reduced nocturnal sleep with daytime sleep [16]. Another study showed that although total nocturnal sleep time is not decreased, the slow-wave sleep (SWS) in narcolepsy is reduced [17].

Although many studies have focused on EDS and cataplexy, few studies have identified the serious sleep fragmentation in nocturnal sleep in narcoleptic patients. In the recently published International Classification of Sleep Disorders, third edition (ICSD-3), few detailed descriptions of disrupted nighttime sleep (DNS) or sleep fragmentation exist. DNS is defined as fragmented sleep during the night, night sleep awakening twice or more for durations longer than 30 minutes, or sleep efficiency less than 90%, and our previous work showed that DNS occurred in 87.7% patients with narcolepsy [18]. In addition, because sleep states are disrupted [19–22], it is essential to determine which sleep stage is most commonly associated with transition into wakefulness. Furthermore, it may be helpful to explain whether frequent REM sleep onset periods alter the ultradian pattern of nocturnal and non-REM (NREM)–REM cycles in narcoleptic patients.

In this study, therefore, we compared the 24-hour sleep architecture, sleep–wake transitions, NREM–REM cycles, and distribution of REM/NREM sleep stages between narcoleptic and control subjects using ambulatory 24-hour polysomnography (PSG). Because all of the subjects were teenagers without any conditions associated with aging, we successfully determined the circadian aspects, ultradian rhythm, and polyphasic transitions in narcolepsy.

2. Methods

2.1. Subjects

This study was approved by the Ethics Committee of Changzheng Hospital. All subjects and their parents gave their informed consent.

Fourteen Han Chinese teenagers (13.4 ± 2.6 years of age, nine male and five female) from the sleep disorder clinic at Changzheng Hospital from July 2015 to September 2015, diagnosed with narcolepsy based on the ICSD-3 criteria [7], were enrolled in this trial. These patients had been either untreated or had withdrawn from stimulant and anti-cataplectic drug therapy for at least 3 weeks prior to this study. A total of 14 healthy age- and sex-matched control subjects (13.6 ± 1.8 years of age, nine male and five female) were also enrolled. The exclusion criteria for all subjects included obstructive sleep apnea syndrome, idiopathic hypersomnia, other sleep disorders, a history of sleep restriction, shift work or jet lag, drug abuse, and additional neurological, psychiatric, or other diseases (especially diabetes and thyroid disease).

All subjects recorded a 7-day sleep log before the trial. Daytime sleepiness was evaluated in all the patients using the Epworth Sleepiness Scale (ESS), from which item 8 was deleted because it is not available for teenagers.

2.2. Protocols

This was a case-control study and was performed at the inpatient PSG wards of the neurology department at Changzheng Hospital (China). The total trial time was 56 hours. Ambulatory PSG was performed for 48 hours starting at 9:30 a.m. on day 1,

followed by a standard 8-hour Multiple Sleep Latency Test (MSLT) on day 3. Day 1 was used for test subjects to adapt to the instruments and to identify and exclude patients with sleep disorders or diseases. Day 2 data were used for analysis.

According to the American Academy of Sleep Medicine (AASM) criteria [23], MSLT was performed with four to five sections on day 3.

Three weeks before the trial, the patients were asked to stop medication; 1 week before the trial, all subjects wore actiwatches and entered data in the sleep log. On the first day of trial, subjects were awakened at 7:30 a.m., and breakfast was served before 8:30 am. The technician began to place electrodes at 9:00 a.m., and the PSG recording began at about 9:30 a.m. of the first day and continued recording without any pause until the end of the trial. During the trial, subjects stayed in the PSG suites and were closely monitored by two authors (X.X. and H.W.). The suites included three separate sleeping rooms for PSG recording, a living room for entertainment, and a bathroom with a toilet. The room temperature was 22 ± 1 °C with a relative humidity of 50–60%. Meals and water were served when they were asked for during spontaneous waking episodes. During the 48 hours of the trial, all subjects were instructed not to resist sleep, and furthermore, to get up and leave the bedroom if they could not fall asleep. They were also instructed to arrange their daily life as usual, and to maintain their routine sleep/wake hours. They were free to use the entertainment room to walk, read, talk, use their cell phones, or iPads/laptops. All subjects were instructed not to consume any caffeinated or alcoholic drinks for at least 6 hours before and during the recording. The sleep log was also used to subjectively record their daily lives and to assess daytime naps and lights off/on during the night.

2.3. Measurements

The 24-hour PSG and MSLT were conducted using an ambulatory polysomnography system (Xltek trex hd, Canada). PSG included electroencephalogram derivations C3/4 and O1/2, referenced to A2/1, respectively, bilateral electro-oculogram, and submental and anterior tibialis electromyograms. Cardiorespiratory data were used initially for excluding other sleep disorders. Data were obtained from two-lead electrocardiography, oro-nasal airflow, breathing

movements by inductive plethysmography, snoring, and arterial oxygen saturation via pulse oximetry.

PSG and MSLT data were mostly scored according to the guidelines of the American Academy of Sleep Medicine (AASM) [23], with the exception of the multiple sleep latency in MSLT. In AASM 2012, the latency of sleep onset is defined as the start of the first epoch scored as any stage other than stage W. In most subjects, this is usually the first epoch of stage N1. However, we found several isolate N1 stage (just one epoch of 15–30 seconds) episodes in some healthy control subjects, but not in narcoleptic patients. The latency of the first isolate N1 cannot reflect real sleep latency. Thus, we used the criteria of Rechtschaffen and Kales [24] for research purposes as “the start of continuous 3 epoch of stage N1 or first epoch scored as any stage other than stage N1.”

To quantify sleep fragmentation and to determine which sleep stage is most commonly associated with transition into wakefulness, we analyzed sleep–wake transitions and the sleep–wake transition rate. Sleep–wake transition (n) is defined as the frequencies of transition to wakefulness from all sleep stages. Sleep–wake transition rate (times per hour, n/h) was identified as the frequency of sleep stage transitions to wakefulness dividing the duration of each sleep state.

To understand the ultradian aspect in narcolepsy type 1, we further analyzed nocturnal NREM–REM cycles (n), NREM–REM cycle rate (n/h), NREM–REM cycle duration (minutes), and nocturnal and 24-hour constituent ratio of REM/NREM sleep stages. We defined the NREM–REM cycles rate as the number of NREM–REM cycles (n) dividing the nocturnal sleep period (hours).

Cerebrospinal fluid (CSF) was collected using lumbar puncture in 14 patients. The samples were immediately frozen and stored at -80°C in an ultra-low-temperature freezer and were sent to Beijing using liquid nitrogen. The Hcrt-1 concentrations were measured by Drs. Han and Li (Beijing People’s Hospital) using an iodine-125 (I^{125}) radioimmunoassay kit (Phoenix Pharmaceuticals, Berlingame, CA, USA) according to the standard methods [25].

2.4. Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as means and standard deviations, and categorical variables were described by numbers or ratio. Comparison of continuous variables was performed using the Student *t* test, except for abnormal distribution of data, which were analyzed using the Mann–Whitney *U* test. A χ^2 test was performed to compare the sex distribution and the sleep onset REM period (SOREMP) occurrence in nocturnal PSG between the two groups. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Characteristics of the 14 patients are shown in Table 1. They include 13 patients with cataplexy, nine with hypnagogic hallucinations, and five with sleep paralysis, who had had narcolepsy for 49.1 ± 25.8 months. The mean ESS score was 13.50 ± 2.74 , and the CSF Hcrt level was 28.05 ± 24.50 pg/mL (Table 2). The control subjects showed comparable sex and age distribution ($p > 0.05$). Compared with the control subjects, patients had higher body mass index (BMI) ($p = 0.001$). During MSLT, the mean sleep latency of patients was 2.04 ± 2.05 minutes and the number of SOREMPs was 2.64 ± 0.75 .

Table 1

Characteristics of the 14 narcoleptic patients.

Patient	Sex	Age (y)	BM I (kg/m ²)	Symptom onset	Disease course (mo)	ESS score	CSF Hcrt -1 (pg/mL)	Other narcolepsy symptoms	Previous use/withdrawal of medications
1	M	12	24.24	EDS	67	16	10.00	Cataplexy, sleep paralysis, complaint of disrupted nocturnal sleep	Methylphenidate, venlafaxine
2	F	13	26.84	EDS	2	14	10.00	Cataplexy, complaint of disrupted nocturnal sleep	None
3	M	16	22.15	EDS	17	16	10.00	Cataplexy, hypnagogic hallucination, sleep paralysis	None
4	F	14	30.47	EDS	67	17	10.47	Cataplexy, hypnagogic hallucination, sleep paralysis, complaint of disrupted nocturnal sleep	None
5	F	12	25.51	EDS	66	12	10.00	Cataplexy, hypnagogic hallucination, complaint of disrupted nocturnal sleep	Methylphenidate, venlafaxine, amitriptyline
6	M	14	23.88	EDS	37	9	16.00	Cataplexy, hypnagogic hallucination, complaint of disrupted nocturnal sleep	Methylphenidate

7	M	14	23.4	EDS	26	13	72.3	Cataplexy, hypnagogic hallucination, sleep paralysis, complaint of disrupted nocturnal sleep	None
		4					0		
8	F	11	24.8	EDS	67	16	10.0	Cataplexy, complaint of disrupted nocturnal sleep	Methylphenidate
		9					0		
9	F	17	20.9	EDS	68	9	10.0	Cataplexy	None
		4					0		
10	M	17	22.1	EDS	66	15	33.6	Cataplexy, hypnagogic hallucination, sleep paralysis	None
		4					3		
11	M	15	29.8	EDS	67	16	51.0	None	None
		6					0		
12	M	10	28.4	EDS	65	10	18.9	Cataplexy, hypnagogic hallucination, complaint of disrupted nocturnal sleep	Venlafaxine
		4					7		
13	M	8	28.2	EDS	5	12	59.3	Cataplexy, hypnagogic hallucination, complaint of disrupted nocturnal sleep	Methylphenidate
		4					0		
14	M	15	27.3	EDS	67	14	71.0	Cataplexy, hypnagogic hallucination, complaint of disrupted nocturnal sleep	None
		4					0		

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; F, female; Hcrt, hypocretin; M, male.

Table 2

Demographic characteristics of narcoleptic patients and control subjects.

	Narcoleptic patients	Control subjects	<i>p</i>
N	14	14	
Male, n (%)	9 (64.29)	9 (64.29)	1.000 ^a
Age, y	13.4 ± 2.6	13.6 ± 1.8	0.868
BMI, kg/m ²	25.60 ± 3.00	21.81 ± 1.79	0.001
ESS	13.50 ± 2.74	5.00 ± 1.11	<0.001
CSF Hcrt, pg/mL	28.05 ± 24.50	NA	NA
MSLT			
Sleep latency,	2.04 ± 2.05	15.60 ± 3.47	<0.001
min	2.64 ± 0.75	0.14 ± 0.36	<0.001
SOREMPs, n			

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; Hcrt, hypocretin; MSLT, multiple sleep latency test; NA, not available; SOREMPs, sleep onset rapid eye movement periods.

Data are expressed in mean ± SD. Significance levels are given (*p*) to compare narcoleptic patients and control subjects.

^a A χ^2 test was used for categorical variables, and a Student *t* test was used for the rest of the data.

3.2. Analysis of sleep architecture

Compared with the control subjects, patients showed significantly longer sleep time over 24 hours (659.86 ± 162.41 vs 437.52 ± 92.84 minutes, $p < 0.001$), and greater duration in N1 (122.93 ± 61.98 vs 21.22 ± 7.86 minutes, $p < 0.001$) and N3 stages (166.54 ± 57.57 minutes vs 100.51 ± 27.56 minutes, $p = 0.001$) than the controls. Patients had more naps (4.86 ± 1.66 vs 0.36 ± 0.50 times, $p < 0.001$), and more SOREMPs (3.21 ± 0.80 vs 0 times, $p < 0.001$). Concentrated circadian hypnograms of all patients and controls obtained from 24-hour PSG are shown in Fig. 1, and two typical detailed hypnograms (narcolepsy patient no. 4 and control subject

no. 1) are shown in Fig. 2.

During nocturnal PSG (Table 3), patients spent more time lying in bed (520.71 ± 77.65 vs 432.17 ± 86.28 minutes, $p = 0.008$), whereas their actual sleep time was not significantly different compared with that of controls (443.43 ± 90.48 vs 412.88 ± 83.57 min, $p = 0.362$). Their sleep efficiency (%) was significantly reduced (84.99 ± 9.34 vs 95.54 ± 1.88 , $p = 0.001$). Patients showed shorter sleep latency (2.88 ± 1.67 vs 10.21 ± 3.24 minutes, $p < 0.001$) and REM latency (34.74 ± 43.76 vs 94.21 ± 23.89 minutes, $p < 0.001$), and more SOREMPs (8 vs 0 person, $p = 0.001$), differing significantly from controls. Patients had significantly more awakenings (29.57 ± 9.22 vs 2.86 ± 1.35 times, $p < 0.001$) and time spent in wakefulness after sleep onset (74.49 ± 50.96 vs 9.44 ± 9.12 minutes, $p < 0.001$). Patients spent more time in N1 stage (64.82 ± 39.36 vs 18.77 ± 7.18 minutes, $p = 0.001$), with a higher arousal index (34.01 ± 16.61 vs 13.64 ± 3.86 , $p < 0.001$) and periodic leg movement in sleep (PLMS) index (19.70 ± 10.14 vs 1.16 ± 1.66 , $p < 0.001$).

Table 3 also shows daytime sleep architecture. The complete dataset derived from daytime PSG includes all of the naps and their duration for each subject included in this study. We found that patients spent significantly more time sleeping during the day (216.46 ± 111.20 vs 70.10 ± 16.01 minutes, $p < 0.001$), and had a higher number of naps with 2.64 ± 0.84 SOREMPs. Nonetheless, only five control subjects had daytime naps without SOREMPs. Compared with the controls, patients' NREM sleep during the daytime was higher, and patients spent significantly longer in N1 (58.11 ± 43.69 vs 7.00 ± 4.81 min, $p = 0.001$) and N3 stages (57.57 ± 42.29 vs 7.00 ± 7.28 minutes, $p = 0.001$).

3.3. Nocturnal sleep–wake transitions

In patients, the frequencies of transition to waking from all sleep stages, in descending order, are as follows: N2 stage to wakefulness (12.29 ± 6.21 times), N1 stage to wakefulness (7.36 ± 5.90 times), REM stage to wakefulness (7.14 ± 4.33 times), and N3 stage to wakefulness (2.79 ± 2.49 times); in controls: N2 stage to wakefulness (1.93 ± 0.73 times), REM stage to wakefulness (0.57 ± 0.65 times), N1 stage to wakefulness (0.29 ± 0.47 times), and N3 stage to wakefulness (0.14 ± 0.36

times). Compared with controls, the frequencies of all sleep stage (N1, N2, N3, and REM) transitions to waking state were significantly higher in patients ($p < 0.001$).

The patient sleep–wake transition rates (times per hour) in descending order are as follows: N1 stage to wakefulness (6.64 ± 3.64), REM stage to wakefulness (5.22 ± 3.18), N2 stage to wakefulness (4.34 ± 2.33), and N3 stage to wakefulness (1.46 ± 1.14); in controls: N2 stage to wakefulness (0.56 ± 0.23), N1 stage to wakefulness (0.50 ± 0.86), REM stage to wakefulness (0.50 ± 0.57), and N3 stage to wakefulness (0.07 ± 0.19). Compared with the controls, the four sleep–wake (N1, N2, N3, REM) transition rates were all significantly higher in patients ($p < 0.001$).

3.4. NREM–REM sleep cycles

Patients showed a significantly higher frequency of nocturnal transition of NREM to REM sleep (7.50 ± 3.28 times) compared with controls (5.21 ± 1.19 times) ($p = 0.026$). We found that the NREM–REM rate was comparable between the two groups (0.87 ± 0.34 vs 0.74 ± 0.16 n/h, $p = 0.212$). We defined the duration of NREM–REM cycle starting with NREM sleep until the end of REM sleep. Therefore, the NREM–REM cycle duration was 96.71 ± 51.82 minutes in patients and 100.86 ± 29.45 minutes in controls, without any significant difference between the two groups ($p = 0.563$).

We also calculated the constituent ratio of REM/NREM sleep stages during night (0.25 ± 0.09 vs 0.30 ± 0.05 , $p = 0.132$) and the 24 hours (0.25 ± 0.12 vs 0.29 ± 0.05 , $p = 0.276$), and found that there were no significant differences between the two groups.

Table 3

Ambulatory PSG parameters of narcoleptic patients and control subjects.

Narcoleptic patients	Control subjects	p
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<i>n</i>	14	14	
24-h PSG			
Total sleep time, min	659.86 ± 162.41	437.52 ± 92.84	<0.001
Total awakening time, min	780.14 ± 162.41	1002.48 ± 92.84	<0.001
Naps, <i>n</i>	4.86 ± 1.66	0.36 ± 0.50	<0.001 ^b
SOREMPs, <i>n</i>	3.21 ± 0.80	0	<0.001 ^b
N1, min	122.93 ± 61.98	21.22 ± 7.86	<0.001
N1%	18.70 ± 9.12	4.75 ± 1.26	<0.001
N2, min	237.79 ± 71.14	218.34 ± 45.99	0.398
N2%	35.77 ± 5.12	49.97 ± 2.85	<0.001
N3, min	166.54 ± 57.57	100.51 ± 27.56	0.001
N3%	26.01 ± 9.14	22.92 ± 3.85	0.261
REM, min	132.61 ± 56.85	97.46 ± 25.26	0.047
REM%	19.53 ± 6.98	22.36 ± 3.33	0.184
Nocturnal PSG			
Sleep latency, min	2.88 ± 1.67	10.21 ± 3.24	<0.001
REM latency, min	34.74 ± 43.76	94.21 ± 23.89	<0.001
SOREMPs, person (%)	8 (57.14)	0 (0)	0.001 ^c
Sleep period time, min	520.71 ± 77.65	432.17 ± 86.28	0.008
Total sleep time, min	443.43 ± 90.48	412.88 ± 83.57	0.362
Sleep efficiency,%	84.99 ± 9.34	95.54 ± 1.88	0.001
W, min	77.36 ± 50.85	19.29 ± 8.89	0.001
N1, min	64.82 ± 39.36	18.77 ± 7.18	0.001
N1%	14.86 ± 9.15	4.46 ± 1.12	0.001
N2, min	179.00 ± 49.01	202.34 ± 38.44	0.173
N2%	40.40 ± 7.74	49.20 ± 2.52	0.001
N3, min	108.96 ± 34.79	97.63 ± 24.31	0.327
N3%	24.82 ± 6.94	23.54 ± 3.24	0.539
REM, min	90.61 ± 39.95	94.11 ± 23.27	0.779
REM%	19.91 ± 5.99	22.81 ± 2.90	0.120
Awakenings, <i>n</i>	29.57 ± 9.22	2.86 ± 1.35	<0.001

Abbreviations: Noc, nocturnal; NREM, non-rapid eye movement; PLMS, periodic leg movement in sleep; PSG, polysomnography; REM, rapid eye movement; SOREMPs, sleep onset in REM periods; W, wake stage; WASO, wake time after sleep onset;

Data are expressed in mean $\pm$ SD. Significance is given (p) to compare narcoleptic patients and control subjects.

^a In daytime PSG, only five control subjects had daytime naps, and their data were analyzed.

^b The Mann–Whitney U test was used for abnormal distribution data.

^c The χ^2 test was used for categorical variables and the Student t test was used for the rest of the data.

Fig. 1. Concentrated circadian hypnograms of all patients and controls; complete data set obtained from 24-hour polysomnography (PSG).

Fig. 2. Twenty-four-hour and nocturnal hypnograms of a patient and a control subject. (a, c) A typical narcoleptic patient with cataplexy, hypnagogic hallucinations, and sleep paralysis: male, 17 years of age, body mass index (BMI) 24.24 kg/m², Epworth Sleepiness Scale (ESS) score 15, disease course 84 months. (b, d) A typical control subject: male, 16 years, BMI 22.34 kg/m², ESS score 3.

4. Discussion

In this case-control study, narcoleptic patients spent significantly more sleep time (~1.5-fold increase) over 24 hours mainly due to increased daytime sleep, while their total nocturnal sleep time was comparable to controls. Furthermore, their SWS and REM sleep increased accordingly, which is different from past studies [26]. As expected, patients had significantly increased numbers of naps and higher SOREMPs during the daytime, consistent with the results of previous studies [27,28]. When we focused on nocturnal sleep, patients showed shorter sleep latency and REM sleep latency, increased light sleep, frequent awakenings, and additional time in wakefulness after sleep onset. Although patients showed obvious sleep fragmentation, the duration of any nocturnal sleep stage, including SWS and REM sleep, was not less than that of the controls.

Although the previous studies have made many discoveries of sleep architecture, sleep stages transition, and NREM–REM cycles in narcolepsy, there are still many points that need to be further clarified. In the current study, we focus on the states of sleep during 24 hours, sleep fragmentation (sleep stages transitioning to wakefulness), and NREM–REM sleep cycles/balance. The purpose and design of this study are different from those of previous studies. Here we compare these studies, including their objectives, methods, results, and conclusions, in Table 4.

The comparisons between the previous studies and our study might strengthen our findings. Our study shows clear evidence of significantly longer sleep time, the characteristics of sleep–wake patterns, both sleep fragmentation and wakefulness fragments, and of the NREM–REM sleep cycles/balance in narcolepsy patients with low Hcrt-1 in CSF. Furthermore, daytime sleep in narcolepsy did not compensate for SWS and REM sleep deficiency at night. It is useful to point out that these patients are Han Chinese. We reported in 2014 that the peak age of narcolepsy in China in children was 8–12 years, which was different from the other reports in the United States (teenagers) and in France (~15 years old). Thus, our study contributes additional literature on the differences among ethnicities.

Hcrt is a well-known neuropeptide enabling the maintenance of stable

sleep–wake transition [4,29–32]. Narcolepsy is an appropriate clinical condition that illustrates the breakdown of the switch mechanism in Hcrt deficiency. According to the nocturnal PSG of our study, the frequencies of all sleep stages transitioning to wakefulness were significantly higher compared with those of controls. The results suggest that every sleep stage in narcolepsy is unstable and disrupted, and narcoleptic teenagers have great difficulty sustaining sleep. Thus, narcolepsy could be better interpreted as both a wakefulness system–disabling and sleep system–disabling disease.

Generally, homeostatic pressure interacts with circadian and ultradian oscillations of sleep propensity, leading to nocturnal distribution and alternate NREM–REM cycles during sleep [33–37]. The 24-hour polyphasic distribution and frequent occurrence of REM sleep onsets in narcolepsy are attributed to altered strength of the homeostatic process or disequilibrium between homeostatic and sleep–wake regulatory rhythms [16,38,39]. Sleep deprivation and bed rest study protocols showed that the homeostatic regulation of sleep is preserved in narcoleptic individuals [16,40–42]. In our study, although patients had more NREM–REM cycles at night compared with controls due to SOREMPs and more time in bed at night, the duration of NREM–REM sleep cycle and constituent ratio of REM/NREM sleep stages were comparable between the two groups. Our data show that narcolepsy may have limited effects on NREM–REM balance, suggesting that ultradian regulation of NREM–REM cycles was also preserved in narcoleptic patients. The findings of the present study provide new evidence to support the hypothesis that sleep ultradian rhythm is coordinately regulated by many neuropeptides, including Hcrt, and histamine, among other substances [43,44].

Limitations of this study relates to the simple analysis of data from 24-hour PSG, without using mathematical or physiological models. Nonetheless, we focused on the sleep architecture and sleep–wake patterns to characterize the circadian aspects and ultradian cycles in narcolepsy. The relatively small sample size might lead to false-negative results. However, the teenage narcolepsy patients involved in our study were Han Chinese individuals who had developed narcolepsy after 2010, which were the years after pH1N1 2009. All the patients were type 1 Narcolepsy with low

concentrations of CSF Hcrt-1. Because the disease course was short, and their ages were close, these patients were well quantified. In addition, the well-matched groups between control and narcoleptic teenagers, and the rigorously controlled experimental conditions, strengthen the reliability of our results.

Table 4.

Comparison between the current study and previous studies.

Study	Objective	Methods	Results	Conclusions	Notes
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Current study	To assess the sleep–wake patterns, sleep fragmentation, and NREM–REM sleep cycles/balance in Chinese teenagers with narcolepsy.	Case-control study Teenagers Groups: NT1 ($n = 14$, ages 8–17 y) vs healthy controls ($n = 14$, ages 11–18 y)	Sleep architecture: 24-h TST: 659.86 ± 162.41 vs 437.52 ± 92.84 min, N3: 166.54 ± 57.57 min vs 100.51 ± 27.56 min, REM: 132.61 ± 56.85 vs 97.46 ± 25.26 min; Nocturnal TST: 443.43 ± 90.48 vs 412.88 ± 83.57 min, N3: 108.96 ± 34.79 vs 97.63 ± 24.31 min, REM: 90.61 ± 39.95 vs 94.11 ± 23.27 min. Sleep fragmentation: N1-W, N2-W, N3-W, and REM-W transitions: 6.64 ± 3.64 vs 0.50 ± 0.86 , 4.34 ± 2.33	Compared with controls, teenage narcoleptic patients showed a 1.5-fold increase in total sleep time over 24 h, characterized by enhanced 24-h slow-wave sleep and 24-h REM sleep. The time of their nocturnal sleep periods of different stages (except N1) was equal to that of the control group. Frequencies of all sleep stage transitions to waking state were	
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Dement et al., 1966 [45]	To identify the characteristic PSG marker in narcolepsy.	Adults Narcolepsy patients ($n = 34$) vs controls ($n = 8$)	34 narcolepsy patients showed sleep attacks, and 24 NC and 1 NwoC showed with SOREMP.	First reported that SOREMP was the characteristic PSG marker of a narcoleptic sleep attack.	No comparison in sleep duration and sleep architecture.
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Billiard et al., 1986 [46]	To identify the daytime sleep characteristics and their relationships with night sleep in narcolepsy.	NC ($n = 36$) Onset age: 5–48 y, recording age: 14–72 y	Analyzed the distribution of SONREM episodes across daytime and found that 12:00-14:00 was the peak level in narcolepsy. Sleep architecture: Nocturnal TST: 493.16 ± 98.33 min, N1: $18.23 \pm 8.38\%$, N2: $52.48 \pm 12.57\%$, N3: $7.79 \pm 4.89\%$, REM: $21.17 \pm 7.61\%$. Daytime TST: 208.41 ± 87.94 min, N1: $18.42 \pm 8.58\%$, N2: $48.03 \pm 12.75\%$, N3: $9.62 \pm 7.60\%$, REM: $23.93 \pm 13.65\%$.	SOREMPs were influenced by a time-of-day effect. TST in NC patients were higher than in general normal population.	No healthy controls. Large span of disease onset and age in patients.
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Tafti et al., 1992 [16]	To identify NREM sleep homeostasis in narcolepsy by acute SD.	Case-control study 24-h SD design Teenagers and adults Nacro ($n = 8$, age: 17–39 y) vs healthy controls ($n = 8$, age-matched)	NREM homeostasis: EEG power density in NREM sleep was elevated in delta and some higher frequencies in both patients and controls, but the response to SD was stronger in narcoleptic subjects. Sleep architecture: The TST in narcolepsy patients were shorter (409.00 ± 23.49 vs 462.31 ± 23.87 min) during the baseline night before SD and much shorter (294.75 ± 48.09 vs $387.19 \pm$	Regulation underlying SWS sleep homeostasis is maintained in narcolepsy. Compared with healthy controls, narcoleptic patients showed a decrease in nocturnal TST before and after 24-h SD.	Small sample study. Original data available before and after 24-h SD.
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Nobili et al., 1995 [41]	To identify dynamics of slow-wave activity in narcoleptic patients under bed rest conditions after 16-h SD.	Case-control study 32-h bed rest protocol after 16-h SD Adults Narco ($n = 9$, age: 22–55 y) vs healthy controls ($n = 9$, age-matched)	Sleep architecture after SD: TST: 1323.7 ± 199.9 vs 1142.8 ± 201.9 min; N1: 231.5 ± 121.2 vs 115.9 ± 45.5 min; N2: 684.4 ± 145.8 vs 666.9 ± 152.2 min; N3: 145.4 ± 59.4 vs 164.8 ± 88.6 min; REM: 261.5 ± 98 vs 194.6 ± 40.5 min	Ultradian drives to sleep seem to be predominant in narcoleptic patients after acute SD. Narcoleptic patients showed an increase of N1 and comparable N2, N3 and REM sleep stages during 32h bed rest protocol after 16h SD.	SD and fixed routine protocol.
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Nobili et al., 2001 [47]	To identify the intra-night sleep dynamics, especially REM sleep cycles of narcoleptic subjects.	Case-control study	Differences consist of the presence of SOREMPs and in a longer duration (120 min vs 90 min) of the NREM–REM cycles.	The longer duration of NREM–REM cycles suggests the dysregulation on REM-ON/REM-OFF and indicates the impairment of ultradian rhythm in narcolepsy.	Abstract, only, was available (not full text)
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Khatami et al., 2007 [48]	To compare EEG dynamics during nocturnal sleep in NC patients and healthy controls.	Case-control study. Teenagers and adults NC patients ($n = 11$, age: 18–37 years) vs healthy controls ($n = 11$, age: 18–41 y)	NREM–REM sleep cycles were longer in NC than controls (128 ± 40 vs 96 ± 19 min)	Fragmented nocturnal sleep is a prominent feature and contributes to excessive daytime sleepiness in NC. Only 3 studies have addressed changes in homeostatic sleep regulation as a possible mechanism underlying nocturnal sleep fragmentation in NC.	
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Vernet et al., 2009 [49]	To isolate and describe a new subtype of narcolepsy with long sleep time.	Cross-sectional study Teenagers and adults Narco with LS ($n = 23$, age: 25.7 ± 10.6 y) vs narco without LS ($n = 29$, age: 30.8 ± 10.1 y) vs IH with LS ($n = 25$, age: 29.6 ± 12.5 y) vs healthy controls ($n = 20$, age: 29.4 ± 8.7 y)	Narco with LS showed similar tetralogy symptoms. They had longer sleep time during 24 h, and higher sleep efficiency, lower ESS scores, and reported that their naps were more often unrefreshing, but their ESS was lower. Sleep architecture: 24 h TST: 738 ± 58 vs 562 ± 66 vs 745 ± 72 vs 564 ± 61 min; Nocturnal TST: 607 ± 61 vs 477 ± 61 vs 655 ± 57 vs 517 ± 60 min Sleep cycle numbers: $6.5 \pm$	Narco with LS showed combined symptoms of both narcolepsy (severe sleepiness) and idiopathic hypersomnia (long sleep time and unrefreshing naps). Thus, they may constitute a group with multiple arousal system dysfunctions. More NREM–REM cycles were shown in Narco with LS and IH with LS, whereas the duration of NREM–REM	Difference in catalogue, could not clarify the characteristics of sleep architecture in narcolepsy type 1 or 2.
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Grimaldi D, et al., 2010 [26]	To identify the circadian rhythm of body core temperature in narcolepsy.	Case-control study 24-h bed rest protocol Adults NC ($n = 10$, age: 38 ± 12 y) vs healthy controls ($n = 10$, age: 44.9 ± 12 y)	BcT: mesor: 36.8 ± 0.12 vs 36.9 ± 0.13 °C, amplitude: 0.36 ± 0.14 vs 0.31 ± 0.15 , acrophase: $16:45 \pm 1:31$ vs $16:43 \pm 1:03$ Sleep architecture: TST: 626.4 ± 124.7 vs 391.8 ± 135.7 min; N1: 119.6 ± 38.5 vs 30.6 ± 23.6 min; N2: 237.55 ± 87.3 vs 184.9 ± 77.6 min; N3: 121.1 ± 38.6 vs 95.0 ± 31.5 min; REM: 148.2 ± 39.7 vs 81.2 ± 37.7 min	Mesor, amplitude, and acrophase of BcT circadian rhythm were comparable in narcoleptics and controls, and no between-group differences were detected in the time-course changes and in the state-dependent modulation at night of BcT. NC patients showed an increase of TST, N1 and REM during 24-h bed rest protocol.	No routine activity, cannot recall their spontaneous sleep time.
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Sorensen et al., 2013 [19]	To determine whether hypocretin deficiency and/or cataplexy predicts the unstable sleep–wake and REM sleep pattern of the human phenotype.	Cross-sectional study Adults NC ($n = 43$, age: 35.3 ± 12.8 y) vs NwoC ($n = 20$, age: 35.4 ± 10.6 years) vs. Narco w normal Hcrt ($n = 20$, age: 33.9 ± 9.9 y) vs. Narco w low Hcrt ($n = 37$, age: 36.2 ± 12.8 y)	Nocturnal TST: 393.0 ± 78.0 vs 418.2 ± 60.5 vs 417.5 ± 54.2 vs 399.8 ± 76.9 min. Sleep–wake transitions: 6.3 ± 2.5 vs 4.1 ± 1.8 vs 4.4 ± 2.0 vs 6.0 ± 2.2 , REM–NREM transitions: 9.0 ± 3.3 vs 7.9 ± 2.4 vs 7.3 ± 1.7 vs 9.2 ± 3.2	Hcrt deficiency and cataplexy show the lower nocturnal sleep time and are both associated with signs of destabilized sleep–wake and REM sleep control.	No healthy comparison groups.
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Pizza et al., 2013 [50]	To compare the features of spontaneous ly occurring daytime sleep episodes at continuous daytime PSG to the MSLT results in the diagnostic assessment of hypersomnia s of central origin.	Cross-sectional study. Teenagers and adults NC ($n = 39$, age: 31.79 ± 15.39 years) vs NwoC ($n = 7$, age: 26.29 ± 6.82 y) vs IH ($n = 19$, age: 43.84 ± 14.10 y) vs sEDS ($n = 33$, age: 38.00 ± 12.42 y)	Two or more SOREMPs of spontaneous daytime sleep had a sensitivity of 75%, with a specificity of 95% for a pathological REM sleep propensity at MSLT. Sleep architecture: Nocturnal TST: 415.69 ± 97.35 vs 412.50 ± 60.37 vs 428.28 ± 62.83 vs 405.06 ± 95.81 min; Daytime TST: 171.17 ± 91.58 vs 97.07 ± 76.96 vs 88.50 ± 73.48 vs 88.86 ± 76.40 min	The occurrence of $\geq$ spontaneous SOREMPs during daytime clearly identified narcoleptic patients, as well as during the MSLT. Daytime sleep time was higher in NC, but no significant between NC and other groups in nocturnal sleep time.	No healthy controls.
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Pizza et al., 2015 [20]	To evaluate the reliability of nocturnal sleep dynamics in the differential diagnosis of central disorders of hypersomnolence.	Cross-sectional study. Teenagers and adults NT1 ($n = 79$, age: 32.77 ± 15.34 y) vs NT2 ($n = 22$, age: 30.32 ± 11.19 y) vs IH ($n = 22$, age: 39.36 ± 12.46 y) vs sHS ($n = 52$, age: 38.37 ± 15.14 y)	Nocturnal TST: 408.19 ± 75.61 vs 418.32 ± 80.3 vs 430.55 ± 58.64 vs 405.65 ± 63.77 min Daytime TST: 165.94 ± 86.03 vs 90.20 ± 79.94 vs 91.11 ± 71.40 vs 102.14 ± 99.89 min tW-S index: 8.12 ± 3.06 vs 4.83 ± 2.13 vs 4.75 ± 2.27 vs 5.43 ± 2.04 , tW-NR-R index: 11.08 ± 3.39 vs 7.47 ± 1.96 vs 7.45 ± 2.44 vs 8.13 ± 2.26 , and tW-N1-NR-R index: 16.03 ± 4.40 vs 7.47 ± 1.96 vs 11.31 ± 3.23 vs 11.84 ± 2.96 .	The comparable nocturnal TST among these groups, whereas NT1 patients showed longer daytime TST. The wakefulness to sleep transition index were higher in NT1. These indexes had a good sensitivity and specificity profile to identify NT1 sleep.	No healthy controls.
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Christensen et al., 2015 [21]	To identify the sleep-stage transitions during PSG recordings as diagnostic features of type 1 narcolepsy.	Cross-sectional study. Adults NC ($n = 155$, age: 50.27 ± 15.32 y) Non-NC ($n = 1218$, age: 49.48 ± 12.53 y)	SOREMP ≤ 15 : Sens: 29.7%, Spec: 99.5%; 5N1W->2R ≥ 5 : Sens: 16.8%, Spec: 98.9%; 3N2N3->2N1W ≥ 22 : Sens: 16.1%, Spec: 96.6%; N1Wbouts ≥ 6 epochs ≥ 16 : Sens: 29.0%, Spec: 96.8%	Increased sleep-stage transitions notably from ≥ 2.5 min of W/N1 into REM are specifically diagnostic for narcolepsy independent of a nocturnal SOREMP.	
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Liu et al., 2015 [22]	To determine the diagnostic values, longitudinal stability, and HLA association of the sleep stage transitions in narcolepsy.	Cross-sectional study. Teenagers and adults NT1 ($n = 35$, age: 24.3 ± 11.7 y) vs NT2 ($n = 39$, age: 28.1 ± 12.7 y) vs relatives ($n = 26$, age: 36.2 ± 15.0 y) vs non-narcoleptic controls ($n = 159$, age: 42.6 ± 14.4 y)	Transition from non-N2/N3 to R: 92% vs 69.4% vs 46.2% vs 39.3%	The highest prevalence of altered transition from non-N2/N3 to REM was found in NT1. Altered sleep stage transition is a significant and stable marker of narcolepsy.	No healthy comparison groups. Focus on sleep stage transition to REM sleep.
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Abbreviations: BcT, body core temperature; ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; IH w LS, IH with long sleep time; Hcrt, hypocretin; Narco w LS, narcolepsy with long sleep time; Narco wo LS, narcolepsy without long sleep time; Narco w low Hcrt, narcolepsy with low Hcrt-1; Narco w normal Hcrt, narcolepsy with normal Hcrt-1; NREM, non-rapid eye movement; NREM and REM sleep, NREM sleep stage 1 (N1), NREM sleep (N2, N3), and REM sleep; NwoC, narcolepsy without cataplexy; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography; REM, rapid eye movement; sEDS, subjective excessive daytime sleepiness; Sens, sensitivity; sHS, subjective hypersomnolence; SOREMPs, sleep onset REM periods; spec, Specificity; -tN1-NR-R, transition between wakefulness; tW-NR-R, transition between wakefulness; tW-S, transition between

wakefulness and sleep; W, wake.

5. Conclusions

In summary, our study delineates the unique circadian aspects and ultradian cycles in Han Chinese teenagers with narcolepsy. Despite having sleep architecture quantities at night that were comparable to those in the healthy controls, the patients showed serious daytime sleepiness, which indicates that daytime sleepiness is seldom caused by nocturnal sleep deficiency. Impaired wakefulness and instability of sleep–wake transitions reflect excessive daytime sleep and nocturnal sleep fragmentation. On the other hand, even though narcolepsy is characterized by frequent SOREMPs, the NREM–REM sleep cycle pattern was investigated briefly in our study, suggesting that ultradian regulation of NREM–REM sleep might be preserved in narcoleptic patients.

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Figure 1