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Abnormal Sleep Microstructure and Autonomic Response in Narcolepsy

Abnormální mikrostruktura spánku a autonomní odpověď u narkolepsie

Summary

The present study was aimed at analysing the non-rapid eye movement (NREM) sleep microstructure by the cyclic alternating pattern (CAP) and at assessing the heart rate variability (HRV) changes in patiens with narcolepsy, hypothesizing a correlation of an abnormal sleep microstructure and abnormal autonomic response with a selective loss of hypocretin-containing neurons in narcolepsy. Fifteen patients with narcolepsy-cataplexy (mean age 35 ± 8.5; age range 22–44), and 15 age and sex matched controls (mean age 31 ± 11.4; age range 19–48) were included in the study. All subjects underwent polysomnography recordings for two consecutive nights in a standard laboratory setting. The sleep scoring was focused on the CAP and HRV analysis. A significant decrease in CAP rate as well as significant reduction of the LF spectral band and the LF/HF ratio, and the elevation of the HF spectral component during NREM 4 stage were revealed in narcoleptics compared to controls. Our results suggest that physiological fluctuation of arousal during sleep described as CAP is impaired in narcolepsy and accompained by reduced sympathetic tone during SWS. We have hypothesized that the whole sleep regulation process is altered in narcolepsy and not only REM sleep mechanisms.

Souhrn

Patofyziologickým podkladem narkolepsie-kataplexie je ztráta hypokretinových neuronů posterolaterálního hypotalamu. Předpokládaným projevem tohoto deficitu je změna mikrostruktury a autonomních funkcí ve spánku u těchto pacientů. Cílem studie bylo hodnocení mikrostruktury NREM (non-rapid eye movement) spánku metodou sledování cyklických alternujících vzorců (CAP) a změny variability srdeční frekvence (HRV). Do studie bylo zahrnuto 15 pacientů s narkolepsií-kataplexií (průměrný věk 35 8,5 věkové rozmezí 22–44 let) a 15 zdravých kontrol (31 ± 11,4; 19–48 let). Obě skupiny podstoupily 2 následná polysomnografická vyšetření, pro analýzu CAP a HRV byla zpracována data ze 2. noci. Prokázali jsme signifikantní snížení CAP, provázené snížením LF a zvýšením HF složky při redukci poměru LF/HF v průběhu NREM spánku. Výsledky vyjadřují poruchu kolísání prahu probuzení u narkolepsie-kataplexie, která je provázena redukcí tonu sympatiku během NREM spánku. Domníváme se, narkolepsie nevzniká pouze v důsledku poruchy regulace REM spánku, nýbrž že je současně vlivem deficientní hypokretinové modulace porušena i regulace NREM spánku.

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Klíčová slova

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Introduction

Narcolepsy with cataplexy is a homogeneous disabling neurological disease linked to the DQB1*0602 haplotype [1] affecting approximately one in 2000 individuals. It is characterized by excessive daytime sleepiness, cataplexy and disturbed nocturnal sleep, often also by hypnagogic hallucinations [2] and sleep paralysis, is related to a severe hypocretin deficiency [3,4,5]. Hypocretin deficiency accounts for REM sleep abnormalities [6,7] but also for non-rapid eye movement (NREM) sleep abnormalities [8].

We have focused on the cyclic alternating pattern (CAP) analysis, which is the natural arousal rhythm of NREM sleep [9,10]. CAP consists of arousal-related phasic events (phase A) that interrupt, at the intervals of 20–40 s, the tonic theta/delta activities of NREM sleep (phase B). Functionally, CAP translates a condition of sustained arousal instability, while the complementary EEG pattern, i.e. non-CAP (NCAP), characterized by a rhytmic background activity reflects a condition of stable arousal. The CAP sequences constitute the microstructural component of sleep that accompanies dynamic shifts between the NREM stages and seems to play its role in the transition from NREM to REM sleep. The physiological balance between CAP and NCAP has been found to be altered in a number of sleep-disturbed conditions [11,12]. CAP and NCAP also have repercussions on motor and vegetative activites. Some relations between these microstructural parameters and autonomic function have been preliminary reported in young adults using the spectral analysis of the heart rate variability during sleep [13] and in children and adolescents [14]. The heart rate is under the control of efferent sympathetic and vagal activities directed to the sinus node, which are modulated by the central brainstem and peripheral oscillators [15], this method allows to analyse the modullatory effects of neural mechanisms on the sinus node, and two main components are currently considered, high-frequency (HF) and low-frequency (LF). The vagal activity is the major contributor to the HF component, while the LF is considered by both vagal and sympathetic influences.

The aim of the study was to assess not only conventional sleep parameters, but also microstructure by analysing CAP and HRV in adult narcoleptic patients.

Patients and Methods

Fifteen patients with narcolepsy – cataplexy (mean age 35 ± 8.5; age range 22–44), and 15 age- and sex-matched controls (mean age 31 ± 11.4; age range 19–48) were included in the study. All subjects had classical history of imperative sleepiness and cataplexy, while the presence of further symptoms was not unconditional. All the patients had findings typical of narcolepsy on overnight polysomnography and the Multiple Sleep Latency Test (MSLT), all of them were HLA DQB1* 0602 positive. The hypocretin level in the cerebrospinal fluid was not measured. None of the patients suffered from other sleep disorders. All medication was discontinued at least 2 weeks before recording (metylphenidate, modafinil).

The control group consisted of healthy volunteers reporting subjectively normal sleep habits, with no complaint of either insomnia or excessive daytime sleepiness, receiving no sedatives or stimulants. All subjects gave informed consent before the investigation.

Polygraphic recording and scoring

Each subject underwent polysomnography recordings for two consecutive nights in a standard laboratory setting, only the data from the second night were analysed further. The polygraphic recording started between 10:00 and 11:00 p.m., and ended by spontaneous awakening between 6:00 and 8:00 a.m., the recordings were made using the standard placement of EEG electrodes (F4–C4, C4–P4, F3–C3, C3–P3, C4–A1, and C3–A2, sampling rate 128 Hz), submental and bilateral anterior tibialis EMG, horizontal electro-oculogram, termistor for recording the respiration, abdominal and thoracic sensors for recording the breathing effort, pulse oxymeter, and infrared video camera. The sleep macrostructure was visually scored according to international criteria [16].

CAPs were visually scored by one scorer [17]. The cyclic alternating pattern is a periodic EEG activity of NREM sleep characterized by repeated spontaneous sequences of transient events (phase A). The return to background activity identifies the interval, that separates the repetitive elements (phase B). CAP A phases are subdivided into a 3-stage hierarchy of arousal strength: A1 with synchronized EEG patterns and mild polygraphic variations; A2 with desynchronized EEG patterns preceded by or mixed with slow high-voltage waves and a moderate increase of muscle tone and/or cardiorespiratory rate; A3 with desynchronized EEG patterns alone and coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate.

In the course of polygraphic recording, the heart rate signal was obtained from a surface pre-cordial ECG lead (sampling rate 500Hz), and the R–R interval sequence was obtained by a computerized algorithm of the ECG registration. The time series trend was calculated, and the non-equidistant time sequence was interpolated using a third grade function – cubic spline – and further sampled at a sampling frequency of 4 Hz. Then a fast–Fourier transformation of the adjusted time series was carried out to determine the power spectral analysis, which was decomposed into the following spectral components: VLF 0.02–0.05 Hz, LF 0.05–0.15Hz, and HF 0.15–0.4Hz. The analysis was performed from repeated ectopic-free intervals of approximately 5 min (256 beats) during (i) 15–20min of the wake state before sleep onset (when the lights were on, and wakefulness was controlled by a technician and by EEG), during (ii) stage 2 NREM sleep, (iii) stage 4 NREM sleep, and (iv) REM sleep. In this way, the whole course of the mentioned sleep stages was analysed, eliminating only the segments containing ectopic beats, movement artefacts or arousal.

Statistical analysis included the analysis of variance (ANOVA), Friedman test, Tukey test (for post–hoc multiple comparison), Student's t-test and Wilcoxon matched paired test. The normal distribution was evaluated using D'Agostino Omnibus test and Shapiro-Wilks test.

Results

Macrostructural polygraphic parameters of narcoleptics and of normal subjects are shown in Table 1. The sleep onset latency and REM sleep latency were both significantly shorter in patients with narcolepsy than in

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normal subjects, narcoleptic patients also showed significantly lower values of sleep efficiency. The number of awakenings per hour, percentage of WASO and that of NREM 1 and REM were significantly higher, while the percentages of NREM 2 and slow-wave sleep (SWS) were significantly reduced in narcoleptic patients.

The comparison between CAP parameters from narcoleptic patients and controls disclosed significantly reduced total CAP rate (i.e. the percentage of NREM sleep occupied by CAP sequences) in our patients with narcolepsy because of its reduction during NREM 2 and SWS. The relative proportion of the different CAP subtypes also differed in our patients because of its reduction in the percentage of A1 subtypes and the increase in A2 and A3 subtypes. This disproportion was due to a selective significant reduction in the number of A1 subtypes/h (A1 index) and, to a lesser extent, a reduction in A3 index. Finally, a significant difference was also found for the average number of CAP sequences, which was smaller in narcoleptic patients than in controls (Table 2).

Table 3 shows the comparison of autonomic response between narcoleptic patiens and healthy controls. There was no significant difference in the assessed part of the VLF spectral band between the groups in any sleep stage. The statistical analysis indicates a significant difference between narcoleptics and control group in LF component, this component being lower in the patient group during NREM 4. In both groups, the individual sleep stages differed in the normalized values of the LF band with

Table 1. Polygraphic macrostructural parameters in narcoleptics and normal subjects.

Parameter	Narcolepsy Mean ± SD	Controls Mean ± SD	p-value (p <)
TST (min)	425.9 ± 75.5	419.5 ± 54.5	NS
SL (min)	5.4 ± 6.1	14.9 ± 11.7	0.03
RL (min)	17.1 ± 31.9	81.6 ± 48.4	0.00001
AWN / h	3.9 ± 1.8	1.6 ± 1.1	0.00001
SE (%)	85.7 ± 12.1	92.5 ± 5.1	0.0004
WASO (%)	13.0 ± 12.1	3.9 ± 3.6	0.00003
NREM 1 (%)	3.9 ± 3.3	1.6 ± 1.9	0.0007
NREM 2 (%)	36.6 ± 11.3	46.1 ± 7.1	0.00003
SWS (%)	19.7 ± 7.9	25.5 ± 7.3	0.001
REM (%)	27.0 ± 8.4	22.9 ± 5.2	0.01

TST: total sleep time, SL: sleep latency, RL: first REM latency, AWN/h: number of awakenings per hour, SE: sleep efficiency, WASO: wakefulness after sleep onset, SWS: slow-wave sleep

Table 2. CAP parameters in narcoleptics and normal subjects.

Parameter	Narcolepsy Mean ± SD	Controls Mean ± SD	p-value (p <)
CAP rate (%)	28.6 ± 13.4	33.8 ± 8.1	0.006
CAP rate NREM 1 (%)	6.2 ± 7.6	7.7 ± 9.6	NS
CAP rate NREM 2 (%)	17.5 ± 11.8	23.3 ± 9.3	0.04
CAP rateSWS (%)	50.8 ± 21.3	59.9 ± 18.6	0.04
A1 (%)	75.4 ± 9.8	81.5 ± 8.3	0.002
A2 (%)	12.1 ± 6.2	9.2 ± 5.1	0.02
A3 (%)	12.5 ± 7.2	9.3 ± 4.8	0.02
A1 index (n,hour)	29.5 ± 14.9	38.0 ± 11.6	0.005
A2 index (n,hour)	5.1 ± 3.2	4.9 ± 2.2	NS
A3 index (n,hour)	2.3 ± 1.7	3.3 ± 2.1	0.02
Number of CAPSequences	22.9 ± 9.3	30.1 ± 7.6	0.0003

CAP rate: percentage of NREM sleep occupied by CAP sequences, A index: number of A subtype per hour

Table 3. Parameters of spectral analysis of HRV during sleep in narcoleptics and normal subjects.

Parameter	Narcolepsy				Controls			
	Wakefulness Mean ± SD	NREM 2 Mean ± SD	NREM 4 Mean ± SD	REM Mean ± SD	Wakefulness Mean ± SD	NREM 2 Mean ± SD	NREM 4 Mean ± SD	REM Mean ± SD
R-R mean (ms)	0.948 ± 0.159	0.986 ± 0.161	0.971 ± 0.146	0.972 ± 0.146	0.962 ± 0.128	1.089 ± 0.135	1.062± 0.141	1.033 ± 0.135
Total power (ms^2)	4010 ± 3698	2893 ± 2047	2112 ± 1626	3874 ± 2956	2237 ± 2167	3403 ± 3326	2815 ± 3346	4085 ± 3924
Rel.VLF (%)	25.2 ± 15.7	15.2 ± 8.0	13.3 ± 9.6	23.0 ± 10.1	19.2 ± 10.2	16.9 ± 9.3	15.9 ± 6.8	26.4 ± 14.4
LF/HF	1.12 ± 0.56	0.79 ± 0.32	0.39 ± 0.27*	1.20 ± 0.75	1.09 ± 0.92	1.15 ± 0.83	1.03 ± 0.83	2.53 ± 2.01
LF (n.u.)	0.49 ± 0.13	0.37 ± 0.11	0.25 ± 0.13*	0.45 ± 0.14	0.45 ± 0.16	0.44 ± 0.17	0.41 ± 0.18	0.57 ± 0.22
HF (n.u.)	0.52 ± 0.12	0.65 ± 0.11	0.75 ± 0.13*	0.55 ± 0.14	0.55 ± 0.16	0.55 ± 0.17	0.58 ± 0.18	0.43 ± 0.22

Rel.VLF = relative value of the VLF component; LF (n.u.), HF (n.u.) = values of the LF and HF components in normalized units
**p < 0.05 vs controls*

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significantly lower values in NREM 4 sleep and in NREM 2 sleep compared to REM sleep in the control group and lower values in NREM 4 sleep compared to wakefulness and REM sleep in the narcoleptics. The difference in HF spectral component between narcoleptics and controls was statistically borderline ($p = 0.05$) – the HF component in normalized units was higher in narcoleptics than in controls in NREM 4 sleep. The other sleep stages and wakefulness did not differ between narcoleptics and controls in this spectral band. In both groups the HF component in normalized units differed significantly between the sleep stages; in controls the HF component was significantly higher in NREM 2 and NREM 4 sleep than in REM sleep; in narcoleptics the HF component was significantly higher in NREM 4 sleep compared to wakefulness and REM sleep. The LF/HF ratio was significantly lower in narcoleptics than in control group during NREM 4, and changed significantly between the individual sleep stages. In controls the LF/HF ratio was significantly higher in REM sleep in comparison with NREM 2, NREM 4 and wakefulness. In narcoleptics, the LF/HF ratio was significantly lower in NREM 4 compared to the wakefulness and REM sleep.

Neither group differed in the total spectrum power in any sleep stage. Statistically significant changes of the total spectrum power between the individual sleep stages were found in both groups of subjects with significantly higher value of the total spectrum power in REM sleep in comparison with NREM 4 sleep.

The group of narcoleptics did not differ in the length of the R–R interval from the control group in any sleep stage or during the wakefulness. The R–R interval length has changed significantly between the individual sleep stages in both groups. In controls, the R–R interval was significantly shorter in wakefulness than in NREM 2, in NREM 4 and in REM sleep. The R–R interval in narcoleptics was also shorter during wakefulness than in the individual sleep stages, but the differences were not statistically significant.

Discussion

While our patients' sleep structure changes are in a good agreement with previous data, NREM sleep microstructure, as reflected by the CAP changes and autonomic response, was significantly impaired. The sleep macrostructural changes found in our narcoleptic patients were expected. In fact, DQB1*0602 positive narcoleptic patients show a reduced REM latency and sleep efficiency, and increased percentage of WASO and stage 1, as well as a reduced amount of stage 2 and SWS [18].

The new finding in our study was a reduced amount of CAP in DQB1*0602 positive narcoleptic patients. CAPs were composed of different transient events indicated as subtypes A1, A2 and A3 [17] which functionally are thought to translate a condition of sustained arousal instability oscillating between greater (phase A) and lesser (phase B) arousal level. Among the different subtypes of the CAP A phases, the most common is A1 characterized by sequences of K-complexes or delta bursts in NREM sleep stages, associated with mild polygraphic variations and activation of somatic and autonomic systems [17,19].

Our results have indicated that the occurrence of this CAP component is impaired during NREM sleep in narcoleptic patients. Thus, narcolepsy is accompained not only by alterations of REM but also NREM sleep which is impaired subtly, but significantly. Our results are in a good agreement with those presented previously [20].

The alteration between sleep and wakefulness seems to be regulated by multiple arousal systems and each of them seems to play a specific role in waking and sleep. Hypocretin appears only to affect nonspecific thalamocortical projection neurons, with no effects on the specific sensory relay thalamic neurons. Hypocretin may thus act in the thalamus to promote wakefulness by exciting neurons of the nonspecific thalamocortical projection system which stimulate and maintain cortical activation via widespread projections to the cerebral cortex. Also in the cortex, hypocretin has been shown to excite a specific subset of cortical neurons, which may be also involved in promoting widespread cortical activation via corticocortical projections [21]. In narcolepsy hypocretin defficiency may reflect in the reduced activity of cortical arousal regions resulting in the reduced CAP rate encountered in NREM sleep.

During sleep, the patient group differed from controls in a higher normalized value of HF component, lower normalized LF component, and lower LH/HF ratio during NREM 4 sleep. In the course of the other sleep stages, the differences in these parameters of HRV between narcoleptics and controls were similar, but did not reach statistical significance. This observation indicates that, compared to normal subjects, in narcoleptics the sympathovagal balance is more shifted towards prevailing parasympathetic influence in stage 4 NREM sleep. From the CAP standpoint, transient slow-wave activity bursts (A1 subtypes) are considered cortical activation events also accompained with autonomic subcortical changes [13,14,19].

Our findings of both microstructural and autonomic alterations may originate in a deficient hypocretin system in narcolepsy [3,22]. The hypocretin neurons in the perifornical region of the hypothalamus not only participate in the regulation of the sleep-wake cycle, but they are also involved in the regulation of autonomic nervous functions [23, 24]. The hypocretinergic fibres are widespread in the hypothalamus, brainstem and spinal cord. Among the sites receiving the hypocretinergic innervation and playing an important role with respect to the cardiovascular regulation there are the paraventricular nucleus in the hypothalamus, nucleus of the solitary tract, rostral ventrolateral area in the medulla oblongata, and intermediolateral column in the spinal cord [25]. The effect of hypocretin on the cardiovascular function probably arises predominantly in the rostral ventrolateral area in the medulla oblongata – hypocretin injected into this region produces hypertension and tachycardia [26,27,28,29].

Autonomic disturbances, such as abnormalities of pupil reactions, sexual dysfunction, or cardiovascular dysregulation in narcolepsy have been described repeatedly [30, 31,32]. Increased blood pressure and decreased heart rate during the onset of cataplexy were documented in literature [33], and the reduced blood pressure reactivity to the handgrip and subnormal sinus respiratory arrhythmia in narcoleptics were observed [31].

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In conclusion, our findings have shown that not only REM but also NREM sleep are significantly altered in narcolepsy. Neurophysiological alterations of NREM sleep microstructure and autonomic alterations in narcolepsy are significant and provide new information on the sleep neurophysiology.

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