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Sleep-Disordered Breathing and Periodic Limb Movements in Narcolepsy with Cataplexy: A Systematic Analysis of 35 Consecutive Patients

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Abstract

Background: Disturbed sleep is a core feature of narcolepsy with cataplexy (NC). Few studies have independently assessed sleep-disordered breathing (SDB) and periodic limb movements (PLMs) in non-homogeneous series of patients with and without cataplexy. We systematically assessed both SDB and PLMs in well-defined NC patients. Methods: We analyzed the clinical and polysomnographic features of 35 consecutive NC patients (mean age 40 ± 16 years, 51% males, 23/23 hypocretin-deficient) to assess the prevalence of SDB (apnea-hypopnea index >5) and PLMs (periodic leg movements in sleep (PLMI) >15) together with their impact on nocturnal sleep and daytime sleepiness using the multiple sleep latency test. Results: 11 (31%) and 14 (40%) patients had SDB and PLMs, respectively. SDB was associated with older age (49 ± 16 vs. 35 ± 13 years, p = 0.02), higher BMI (30 ± 5 vs. 27 ± 6, p = 0.05), and a trend towards higher PLMI (25 ± 20 vs. 12 ± 23, p = 0.052), whereas PLMs with older age (50 ± 16 vs. 33 ± 11 years, p = 0.002) and reduced and fragmented sleep (e.g. sleep efficiency of 82 ± 12% vs. 91 ± 6%, p = 0.015; sleep time of 353 ± 66 vs. 395 ± 28, p = 0.010). SDB and PLMs were also mutually associated (p = 0.007), but not correlated to daytime sleepiness. Conclusions: SDB and PLMs are highly prevalent and associated in NC. Nevertheless, SDB and PLMs are rarely severe, suggesting an overall limited effect on clinical manifestations.

Introduction

Narcolepsy with cataplexy (NC) is characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hallucinations. NC is a hypersomnia of central origin, pathophysiologically associated with the loss of hypocretin (orexin) producing neurons in the hypothalamus [1].

Besides EDS with daytime naps, NC patients typically suffer from nocturnal sleep fragmentation with reduced sleep efficiency, numerous awakenings and larger representation of wakefulness after sleep onset and of non-REM (NREM) sleep stage 1, resulting in a total sleep time per 24 h which is comparable to controls [2]. Comorbid sleep-disordered breathing (SDB) [3–5] and periodic limb movements (PLMs) [6–10], both poten-
tially enhancing nocturnal sleep disruption, frequently occur in NC patients. Surprisingly, PLMs and SDB have never been adequately addressed together in NC: most studies evaluated non-homogeneous populations of narcoleptic patients with and without cataplexy [4, 7, 8, 11], or lacking hypocretin-1 measurements [5, 9, 10]; others did not synchronously assess movement and respiratory disturbances during sleep [3, 4, 9, 10], or applied arbitrary definitions of these sleep disorders [3, 4, 6–8, 11] (online supplementary table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000348719).

According to the guidelines on narcolepsy treatment of the European Federation of Neurological Societies (EFNS) and of the American Academy of Sleep Medicine (AASM) [12, 13], coexistent sleep disorders must be taken into consideration and treated separately along with the specific narcolepsy therapy. Nevertheless, only few studies disclosed a negative impact of SDB and PLMs on nocturnal sleep continuity [6, 10, 11] or, even less, on EDS [10, 11].

The aim of the present study was therefore to investigate the prevalence and the clinical relevance of SDB and PLMs in a clinically homogeneous series of 35 consecutive NC patients.

Patients and Methods

We analyzed sleep data (nocturnal videopolysomnography (VPSG) and multiple sleep latency test (MSLT)) of 35 consecutive new NC patients, referred to the Department of Neurology, University Hospital of Zurich (where the study was conducted) over 3 years. NC was diagnosed according to the International Classification of Sleep Disorders, 2nd edition (ICSD-2) [1]. Data collection was authorized by the local ethics committee, and patients signed a written informed consent. Patients, 51% males, had a mean age of 40 ± 16 years and a mean body mass index (BMI) of 28 ± 6. In all patients, clinical examination and cerebral MRI were normal. They underwent a VPSG followed by MSLT and completed the Epworth Sleepiness Scale (ESS) for subjective EDS assessment [14]. 33 patients were HLA-DQB1*0602-positive (not available in 1 patient, 1 was DRB1*15-positive), and 23 individuals, who underwent lumbar puncture, were hypocretin-1-deficient. 29 subjects were drug-naive (diagnostic assessment), and 6 subjects were recorded after a washout period of 14 days from stimulant (3 patients), anticycatptic (2 patients) or combined (1 patient) treatment.

VPSG was scored according to international scoring criteria [15], and leg movements associated with termination of a respiratory event were systematically excluded [16]. According to ICSD-2, patients with an apnea-hypopnea index (AHI) ≥5/h were considered to have SDB, and individuals with an index of periodic leg movements in sleep (PLMI) ≥15/h to have PLMs [1]. Conforming to AASM criteria, we further differentiated the severity of SDB into mild (AHI between 5 and 15/h), moderate (AHI between 15 and 30/h) and severe (AHI >30/h) [17]. A preliminary comparison was performed between patients with proved hypocretin-1 deficiency and patients who did not undergo lumbar puncture. Clinical and VPSG features of patients with and without SDB and with and without PLMs respectively were compared by means of non-parametric statistical analyses (Mann-Whitney U test, Pearson χ² test). A p value <0.05 was considered statistically significant.

Results

The comparison between NC patients without and with available hypocretin assessment did not show significant differences but higher BMI and respiratory indexes in the subgroup lacking hypocretin-1 measurement, without reaching statistical significance for SDB prevalence (online suppl. table 2).

Eleven patients (31%) were affected by SDB (fig. 1). Mild SDB was diagnosed in 4 (11%) subjects, moderate SDB in another 4, and severe SDB in 3 (9%). In 5 out of 11 (46%) SDB patients, apneas were mostly obstructive, whereas in a single subject mostly of central origin. The remaining 5 patients (46%) showed mixed, obstructive and central apneas. In 2 women with moderate and severe obstructive SDB, apneas and hypopneas were mostly associated with REM sleep, whereas in the other 9 patients, apnea episodes mainly occurred during NREM sleep stages 1 and 2.

NC patients with SDB were significantly older, had a higher BMI, and showed a trend towards higher PLMI that was significant during light NREM sleep, than subjects without SDB. Additionally, SDB patients had a tendency towards larger amounts of NREM sleep stage 1 and less slow wave sleep. We could not detect any difference in gender distribution nor in EDS, although SDB was more often observed in males than in females (table 1).

Fourteen subjects (40%) had PLMs (fig. 1). We observed PLMs during REM sleep in 9 subjects, 1 of them with PLMs selectively during REM sleep (mean PLMI = 2). PLMs subjects were older than patients without PLMs without any other significant clinical differences. PLMs patients showed higher oxygen desaturation index, higher hypopnea index, lower sleep efficiency, longer REM latency, less total sleep time, a lower amount of NREM sleep stage 2, and less sleep-onset REM periods in the MSLT than patients without PLMs (table 1).

Finally, SDB was associated with PLMs (p = 0.007, χ² test) (fig. 1). Indeed, SDB patients showed higher
PLMI in light NREM sleep and a trend towards overall higher PLMI versus NC patients without SDB, whereas PLMs patients had a higher oxygen desaturation index (ODI) and hypopnea index compared with NC patients without PLMs. Moreover, PLMI positively correlated with ODI (Spearman’s correlation coefficient = 0.46; p = 0.005), but not with AHI. Neither SDB nor PLM were significantly associated with drug treatment (table 1).

Discussion

Our study adopted for the first time currently accepted criteria to synchronously assess SDB and PLMs in a clinically homogeneous population of narcoleptic patients with cataplexy free of medication and with hypocretin deficiency. We obtained the following main findings: (1) SDB and PLMs are highly prevalent and mutually associated in NC, especially in older patients; (2) SDB and PLMs are rarely severe in NC, and (3) SDB and PLMs enhance nocturnal sleep disruption without clinically relevant correlations with daytime symptoms.

The prevalence of SDB in our NC population (11/35, 31%) is higher than in the general population [1], but this is in line with the reported prevalence (33/133, 25% with AHI >10/h) in the only study performed in NC patients [5]. The association of SDB with older age [11, 5] and higher BMI [18] in NC mirrors the knowledge of SDB risk factors obtained in the general population [1, 19], but is not sufficient to explain such a high SDB prevalence. Additionally, our predominantly obstructive (and mixed) SDB argue – together with the findings of Sansa et al. [5] – against older findings of mainly central apneas [4], and further support the comorbidity of NC with mild to moderate nocturnal breathing disturbance [7, 8].

Besides the intrinsic relation between BMI and SDB via upper airway obstruction, other pathophysiological mechanisms may explain the increased prevalence of SDB in NC compared to that expected in the general population. Indeed, experimental models showed that hypocretin knockout mice have blunted hypercapnic ventilatory response during wakefulness with increased sleep apneas [20], and reduced long-term facilitation after exposure to intermittent hypoxia [21]. Moreover, hypocretin neurons are activated by CO2 inhalation [22], and increase pre-inspiratory hypoglossal motor activity thus decreasing upper airway resistance during inspiration [23].

Fourteen (40%) out of our NC patients have PLMs, a prevalence significantly higher compared to that of the general population and comparable with the two previous reports [9, 10], further corroborating the evidence of motor control impairment during both NREM and REM sleep in NC. In this context, the association between SDB and PLMs is a new finding in NC (online suppl. table 1), possibly arising from sleep-wake instability typical of NC and further contributing to the fragmentation of nocturnal sleep. The association between PLMs and SDB may also reflect co-shared patho-

![Figure 1](https://example.com/f1.png)

**Fig. 1.** Distribution of SDB (a), PLM severity (b), and association between SDB and PLM (c) in the 35 NC patients.
physiological pathways as suggested by the persistence of PLMs in sleep apnea patients after continuous positive airway pressure treatment and by the recent evidence of their disappearance after a further increase of continuous positive airway pressure titration [24]. Further research is warranted to assess whether PLMs associated with apneas’ terminations (excluded from PLMs criteria) may be due also to intrinsic periodic phenomena. Nevertheless, the contribution of these two disorders to EDS in NC appears to be negligible. Intriguingly, patients without PLMs showed a mildly higher number of sleep-onset REM periods at the MSLT, a finding potentially linked to a negative correlation between sleep-onset REM periods and age (Spearman’s correlation coefficient: −0.47, p = 0.010), as already reported [25].

Our data further suggest that only a minority of NC patients have severe SDB or PLMs. Nevertheless, the two comorbidities should be treated whenever possible [12, 13], in light also of their potential contribution to cardiovascular risk [26, 27].

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

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**Table 1.** Demographic, polysomnographic and MSLT data of NC patients

<table>
<thead>
<tr>
<th></th>
<th>AHI &lt;5 mean SD</th>
<th>AHI &gt;5 mean SD</th>
<th>p value</th>
<th>PLMI &lt;15 mean SD</th>
<th>PLMI &gt;15 mean SD</th>
<th>p value</th>
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<td></td>
<td></td>
<td>21 14</td>
<td></td>
<td></td>
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<td>Males, %</td>
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<td>ns</td>
<td>43 64</td>
<td></td>
<td>ns</td>
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<td>Age</td>
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<td>32.9 11.0</td>
<td>50.2 16.1</td>
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<td>Drug treatment, %</td>
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<td>ns</td>
<td>14 21</td>
<td></td>
<td>ns</td>
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<td>BMI</td>
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<td>ns</td>
<td>15.0 3.4</td>
<td>17.2 4.6</td>
<td>ns</td>
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<td>TST, min</td>
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<td>371.9 52.1</td>
<td>ns</td>
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<td>352.6 66.5</td>
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<td>SE, %</td>
<td>88.2 10.4</td>
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<td>ns</td>
<td>91.3 5.6</td>
<td>82.1 12.4</td>
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<td>ns</td>
<td>14.1 12.3</td>
<td>11.9 20.4</td>
<td>ns</td>
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<tr>
<td>REM L, min</td>
<td>25.3 45.4</td>
<td>103.2 149.8</td>
<td>ns</td>
<td>15.3 28.5</td>
<td>101.6 135.5</td>
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<td>NREM1, %</td>
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<td>21.3 11.7</td>
<td>ns</td>
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<td>20.5 10.6</td>
<td>ns</td>
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<td>NREM2, %</td>
<td>41.4 8.6</td>
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<td>36.2 10.9</td>
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<td>NREM3, %</td>
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<td>ns</td>
<td>14.1 5.8</td>
<td>9.5 7.1</td>
<td>ns</td>
</tr>
<tr>
<td>REM, %</td>
<td>18.4 7.1</td>
<td>17.1 11.1</td>
<td>ns</td>
<td>19.0 7.2</td>
<td>15.9 9.9</td>
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<td>Central AI</td>
<td>0.1 0.3</td>
<td>3.1 5.4</td>
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<td>1.3 4.1</td>
<td>0.6 0.9</td>
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<td>&lt;0.0001</td>
<td>0.7 2.5</td>
<td>0.9 1.9</td>
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<td>&lt;0.0001</td>
<td>1.2 2.5</td>
<td>3.2 5.8</td>
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<td>Hypopnea index</td>
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<td>6.0 7.7</td>
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<td>10.8 13.7</td>
<td>ns</td>
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<tr>
<td>Mean SpO2</td>
<td>95.7 1.2</td>
<td>94.4 1.1</td>
<td>0.008</td>
<td>95.7 1.3</td>
<td>94.8 1.2</td>
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<tr>
<td>Minimum SpO2</td>
<td>89.5 2.8</td>
<td>84.8 3.6</td>
<td>0.001</td>
<td>88.8 3.7</td>
<td>86.9 3.7</td>
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<tr>
<td>ODI</td>
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<td>15.0 11.1</td>
<td>&lt;0.0001</td>
<td>4.2 8.7</td>
<td>8.1 8.9</td>
<td>0.007</td>
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<tr>
<td>Arousal index</td>
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<td>ns</td>
<td>10.8 5.8</td>
<td>11.4 6.7</td>
<td>ns</td>
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<tr>
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<td>12.3 23.0</td>
<td>25.4 19.8</td>
<td>0.052</td>
<td>1.3 2.6</td>
<td>40.7 17.7</td>
<td>&lt;0.0001</td>
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<td>22.1 17.5</td>
<td>0.014</td>
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<td>33.3 23.3</td>
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<td>PLMI in NREM2</td>
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<td>&lt;0.0001</td>
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<td>PLMI in NREM3</td>
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<td>1.5 5.7</td>
<td>108.1 91.2</td>
<td>&lt;0.0001</td>
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<tr>
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<td>6.8 10.3</td>
<td>ns</td>
<td>0.4 1.6</td>
<td>6.8 8.8</td>
<td>&lt;0.0005</td>
</tr>
<tr>
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<td>1.8 1.3</td>
<td>ns</td>
<td>2.0 1.6</td>
<td>1.9 1.3</td>
<td>ns</td>
</tr>
<tr>
<td>MSLT REM L, min</td>
<td>3.6 2.1</td>
<td>5.4 3.7</td>
<td>ns</td>
<td>3.6 1.9</td>
<td>5.2 3.7</td>
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<tr>
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<td>ns</td>
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<td>2.9 1.1</td>
<td>0.035</td>
</tr>
</tbody>
</table>

TST = Total sleep time; SE = sleep efficiency; SL = sleep latency; REM L = REM latency; AI = apnea index; SpO2 = peripheral oxygen saturation; SOREMPs = sleep-onset REM periods.
References


