Obesity accompanies narcolepsy with cataplexy but not narcolepsy without cataplexy

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Abstract

BACKGROUND: Narcolepsy with cataplexy (NC) differs from narcolepsy without cataplexy (NwoC) in the cerebrospinal fluid levels of hypocretin. Since hypocretin is known to regulate not only wakefulness but also eating behaviour, we decided to compare the two entities for body mass index (BMI) and the presence of obesity.
METHODS: Clinical data on patients with NC and NwoC was studied and examined, including nocturnal polysomnography and the Multiple Sleep Latency Test (MSLT). The results were rated against a group of age- and sex-matched healthy controls.
RESULTS: The BMI in NC (29.1±SD=5.8) was significantly higher than in NwoC (25.4±4.4) or in the controls (25.8±3.9) (p<0.001, F=17.4, df= 323), while no difference in BMI was found between NwoC and the controls. The proportion of patients with BMI >30 was significantly greater in NC (39.0%) than in NwoC (13.8%) or than in the control group (13.0%). A negative correlation of BMI and sleep latency in MSLT (p=0.009) was found in the combined NC and NwoC groups.
CONCLUSION: Unlike NC, NwoC has neither a higher BMI nor a higher incidence of obesity than the general population.

Abbreviations:

BMI	- body mass index
CSF	- cerebrospinal fluid
ESS	- Epworth sleepiness scale
HLA	- human leukocyte antigen
MSLT	- Multiple Sleep Latency Test
MSLT-SL	- MSLT - mean sleep latency
NC	- Narcolepsy with cataplexy
N.S.	- non significant
NwoC	- narcolepsy without cataplexy
OSA	- obstructive sleep apnoea
PLMS	- periodic limb movements in sleep
RLS	- restless legs syndrome
SD	- standard deviation
SOREMp	- sleep onset REM (rapid eye movement) periods

ORIGINAL ARTICLE

INTRODUCTION

Narcolepsy with cataplexy (NC) and narcolepsy without cataplexy (NwoC) are disabling neurological diseases marked by excessive daytime sleepiness. Together, they affect 0.03–0.1% of the general population in Western Europe and North America (NC being more prevalent than NwoC). An increased aggregate rate of obesity in the two forms of narcolepsy is mentioned by a number of authors (Cave 1931; Daniels 1934; Thiele & Bernhardt 1933; Roth 1957). NC alone was examined later in some of the more detailed studies of the incidence of obesity and the body mass index (BMI). A significantly higher BMI was repeatedly found in patients with NC than in controls (Schuld *et al.* 2000; Dahmen *et al.* 2001; Schuld *et al.* 2002; Kok *et al.* 2003; Okun *et al.* 2002). Indeed, the idea of NC patients´ propensity for obesity appears to be commonly accepted. NC symptoms arise from the loss of hypocretin neurons in the lateral hypothalamus. Hypocretins have an important role to play in keeping us awake and interestingly, hypocretins influence our eating behavior and metabolism as well (Adamantidis & de Lecea 2009), since the central administration of hypocretin increases daytime food and water intake and metabolic rate dose-dependently (Sakurai 2002). Obesity in narcolepsy can hardly be explained by greater energy consumption, as only one study found higher energy intake in NC subjects than in controls (Bruck 2003) and two studies report lower energy intake in NC (Lammers *et al.* 1996; Chabas *et al.* 2007).

We wondered if the rate of obesity and average BMI is likewise increased in patients with NwoC because, in contrast to NC, hypocretin 1 levels in the cerebrospinal fluid (CSF) are seldom decreased in NwoC (Mignot *et al.* 2002).

MATERIAL & METHODS

We analysed the clinical records of adults with NC and NwoC who received complete clinical examination at our centre between 2005 and 2010. The examination included nocturnal polysomnography and Multiple Sleep Latency Test (MSLT). All of the cohort suffered from daily excessive daytime sleepiness for 3 or more months. While those with NC exhibited straightforward cataplexy, no cataplexy was reported by patients treated for NwoC. MSLT revealed a mean sleep latency (MSLT-SL) of ≤8 min and two or more sleep onset REM periods (SOREMp). Both NC and NwoC were diagnosed in compliance with the International classification of sleep disorders, second edition (American Academy of Sleep Medicine 2005).

Enrolled in the study were only subjects with an unambiguous diagnosis of narcolepsy free from any other neurological involvement which could influence the symptoms of the disease and/or metabolism with the exception of the restless legs syndrome (RLS), periodic limb movements in sleep (PLMS) and obstructive sleep apnoea (OSA).

Eighty-two patients with NC, 29 with NwoC and 215 healthy controls were enrolled. The controls (healthy blood donors) were matched for sex and age in both groups of patients.

The following information was selected and processed from the clinical records of all patients: age at data collection, age at the onset of symptoms, body height and weight, Epworth sleepiness scale (ESS) score, MSLT-SL, number of SOREMp during the MSLT, the presence of OSA (apnoea-hypopnoea index ≥5), and the presence of RLS and/or PLMS (PLMS index ≥15).

The body mass index (BMI) was determined by dividing the weight (in kg) by the height (in m) squared.

The data were processed with the χ-square test when comparing dichotomous data such as presence of obesity as defined by BMI>30. For comparison of continuous data such as ESS or BMI, we used two group t-test with separate variance estimation, and one-way ANOVA. Correlation analysis of the same parameters was performed using Pearson´s parametric methods. The results are presented as mean value ± standard deviation (SD), unless otherwise indicated. The power analysis was performed by Russ Lenth's power and sample-size calculator (2006–2009), all other tests were used as implemented in the statistical package STATISTICA 9 (Statsoft inc, Tulsa, OK, USA)

RESULTS

The demographic data of the three groups, age at examination (age at data collection) and age at disease onset are shown in Table 1. The two groups of patients had a very similar age at disease onset and at data collection, and, consequently, also a similar duration of their disease.

No difference in the occurrence of OSA or RLS/PLMS was found between the groups of patients with NC and NwoC.

The sleepiness-related data, BMI and obesity-related data are shown in Table 2. Patients with NC were found to have a greater average ESS score and a shorter MSLT-SL than those with NwoC. The average number of SOREMp was not significantly larger in the NC group than in the NwoC group.

The mean BMI in patients with NC was significantly higher than in those with NwoC or in the controls (p<0.001, F=17.4, df= 323), while no difference in BMI was found between NwoC and the controls. Similarly, the NC group was found to have a significantly greater proportion of obese patients (BMI >30) and overweight patients (with BMI >25) than the NwoC or control groups. As for the NwoC and control groups, there was no difference in the share of persons with obesity or those with BMI >25.

A negative correlation of BMI and MSLT-SL (p=0.009) was seen in the combined NC and NwoC groups (Figure 1). A similar BMI - MSLT-SL correlation was discovered in the NC group (p=0.046). No such correlation appeared to be present in the group of

patients with NwoC, though it could not be ruled out with respect to the small size of the cohort.

There was no evidence of a correlation between the ESS score and BMI. Nor was any correlation found between the BMI and the number of SOREMp or between BMI and the age at the onset of narcolepsy, the disease duration and/or the age at examination.

DISCUSSION

This study is the first to prove that patients with NC have a higher BMI than those with NwoC, and that patients with NC have a markedly greater incidence of being obese and overweight than patients with NwoC. This is in contrast to Roth´s (1980) estimate that the BMI is the same for both "monosymptomatic and polysymptomatic" narcolepsy and to Chabas´s (2007) result on a small sample of a mere 13 patients. It is worth recollecting that Poli *et al.* and Kok *et al.* found a significantly higher BMI in patients with NC than in those with idiopathic hypersomnia (Kok *et al.* 2003; Poli *et al.* 2009), a disease also characterised by excessive daytime sleepiness but without any evident change of CSF hypocretin level.

The fact that BMI correlates with daytime sleepiness measured by MSLT in narcolepsy (NC and NwoC taken together) was first mentioned in our previous study (Nevsimalova *et al.* 2009). This study replicates this correlation on a partially different patient sample and shows that this correlation also exists in a smaller sample of subjects suffering only from NC. These correlations suggest a tight relationship between the pathophysiological mechanism of sleepiness and the tendency toward obesity in narcolepsy.

Quite a few studies carry documentary evidence of the fact that in the non-selected general population, obesity and excessive daytime sleepiness develop in parallel. While sleep apnoea is regarded as the principal determinant of sleepiness in the obese, there are also reports of obese subjects´ sleepiness associated with sleep loss, depression, metabolic disturbances and lack of physical activity (summed up in Vgontzas *et al.* 2008). According to Vgontzas *et al.* (2008), sleepiness in non-narcoleptic subjects is associated with metabolic disturbances unless it is caused by respiratory disorders in sleep. It is difficult to presume a similar dominant association in NC where the absence of hypocretin transmission is regarded as the primary cause of sleepiness and obesity (Nishino *et al.* 2001) despite its inverse effect on food – hypocretin increases the food consumption. However, other mechanisms of the development of obesity appear to be involved in NC as well. While Nishino *et al.* found a correlation between BMI and leptin levels in the cerebrospinal fluid (Nishino *et al.* 2001), Arnulf *et al.* (2006), referring to their own data, regard any connection between leptin and increased BMI as unimportant. Our study was not designed to estimate the quality of nocturnal sleep so it can hardly reveal any hypothetical interdependence between obesity and poor-quality nocturnal sleep in NC.

Tab. 1. Demographic and sleep disorder–related characteristics.

	NC	NwoC	*p*-value	Controls
Patients total number	82	29		215
Men	37 (45.1%)	14 (48.3%)	N.S.	103 (47.9%)
Women	45 (54.9%)	15 (51.7%)	N.S.	112 (52.1%)
Age	44.9 (17.3)	45.3 (17.9)	N.S.	44.8 (8.3)
Disease onset	22.7 (11.6)	26.0 (15.5)	N.S. (0.3)	

N.S. – non significant

Tab. 2. Sleepiness and daytime sleep-related data and BMI and obesity-related data.

	NC	NwoC	*p*-value	Controls
ESS score	18.5 (3.3)	15.6 (2.5)	<0.001	
MSLT–SL (min)	2.4 (1.8)	3.5 (2.3)	0.01	
MSLT number of SOREMp	3.6 (1.2)	3.2 (1.1)	N.S.	
BMI kg/m^2	29.1 (5.8)	25.4 (4.4)	<0.001	25.8 (3.9)
Number of subjects with BMI >30	32 (39.0%)	4 (13.8%)	0.01	28 (13.0%)
Number of subjects with BMI >25	63 (76.8%)	14 (48.3%)	0.004	119 (55.3%)

N.S. – non significant

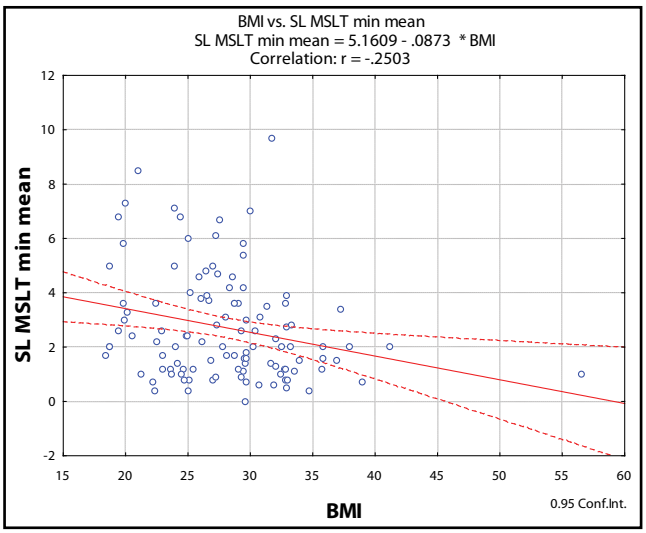

Fig. 1. Correlation of BMI and MSLT-SL in the combined NC and NwoC groups.

The results of our study are the first to show that, in terms of BMI and the incidence of obesity, adult patients with NwoC are in no way different from the

general population. That, however, is in contrast to the idea of NwoC being caused by a partial loss of hypocretin cells (Thannical *et al.* 2009). On the other hand, the study correlating sleepiness with BMI also included patients with NwoC, which is why it is possible to anticipate a more subtle BMI-sleepiness correlation in those patients as well. Hence the need for launching studies of larger cohorts of patients so as to prove or refute any such correlation in NwoC. Our own cohort is statistically strong enough (80%) to record a BMI difference of an absolute value of 2.19. Our study is in disagreement on this point with Kotagal *et al.* (2004), who report a higher BMI in 31 narcoleptic children than in the controls regardless of whether or not they had cataplexy.

However our study has several limitations, in particular, a small number of patients with NwoC. Our patients were diagnosed solely by standard clinical and polysomnographic criteria but the CSF hypocretin levels were not analysed. The Arnulf *et al.* study (2006) describes groups of narcoleptics with and without hypocretin deficiency. The group of patients with normal hypocretin had a slightly lower BMI (and a slightly lower ESS score) than those with CSF hypocretin deficiency, though the difference was not analysed for significance. Our study was not designed to rate the patients´ physical activity regimen or energy input and output, which also modify the BMI. Medication was not taken into account, since two studies found that drug treatment for narcolepsy had no relevance to BMI (Schuld *et al.* 2002, Kok *et al.* 2003). The HLA DQB1*0602 status was not taken account in our study as well because Hong *et al.* could not prove any BMI difference between DQB1*0602 positive and DQB1*0602 negative patients although they used a large group of patients with NC and a similarly large group of patients with NwoC (Hong *et al.* 2000).

CONCLUSION

There is an essential difference between NwoC and NC in the occurrence of obesity and in BMI, i.e., factors which are the same as in the general population in the former while, in contrast, elevated in the latter. This finding substantiates the need for more research effort designed to compare the incidence and pathophysiology of metabolic disorders in NC and NwoC.

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