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Increased prevalence of obesity in narcoleptic patients and relatives

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Abstract Increased Body Mass Indices (BMIs), increased prevalences of non insulin-dependent diabetes and sleep apnoe syndrome have been reported to be associated with narcolepsy. Our objective was to explore and possibly confirm the association of narcolepsy and increased BMI. In addition, we addressed the question whether increased BMIs also occur in relatives of narcoleptic patients. Together with narcolepsy-related clinical parameters we measured body weight and height of 132 narcoleptic patients who agreed to participate in our narcolepsy research program. In addition, 52 first degree relatives of 22 index patients, mostly from multiplex families, were included in the study. Data were compared to published general population surveys, recently conducted in Germany and Switzerland as well as to collective of 104 psychiatric inpatients. Narcoleptic patients had significantly increased BMIs in comparison to general populations or psychiatric controls. BMIs of first degree relatives were lower than those of index patients but significantly higher than those found in the general population. BMIs were not related to symptom severity or to medication status. Thus, the elevated BMIs appeared not to be secondary to behavioral consequences of narcolepsy but may reflect a trait at least partially common to index patients and relatives.

Key words Narcolepsy · Obesity · Body mass index · Orexin · Family study

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Introduction

Narcolepsy is conceptualized as a dysregulation of different sleep and wake stages. Its main symptoms are irresistible daytime sleepiness, sleep attacks, sometimes preceded by episodes of automatic behavior and so-called REM-associated symptoms such as cataplexies, sleep related hallucinations and sleep paralysis.

It has been noted that narcoleptic patients tend to be more obese than population controls [15, 26]. Although relevant to the psycho-social well-being of many narcoleptic patients, the relation between obesity and narcolepsy has not attracted a great deal of scientific interest and the early findings were not replicated in adequate samples. If the reported associations are true, the question arises whether increased measurements of obesity ought to be viewed as a primary symptom of narcolepsy or as secondary to disease-related changes and adjustments. For example, reduced locomotion, avoidance of sports, preference to stay home or increased food intake due to a hypothetical relative lack of non-food reward could be plausible explanations for the occurrence of obesity in narcoleptic patients. Alternatively, obesity in general or specific subtypes of obesity could predispose to narcolepsy. Apart from the theoretical interest, the exploration of this question may also be justified by the fact that many of our patients expressed grief about their body weight and some have undergone specific psychotherapy aimed at their presumed eating disorder. Because the medications used in the treatment of narcolepsy may affect appetite and food intake, the interaction of medication and body weight needs to be specifically addressed in narcoleptic patients.

Recently the hypothalamic orexin system has been implicated in the pathophysiology of narcolepsy by studies conducted in narcoleptic dogs [17], orexin-deficient transgenic mice [5] and by orexin measurements in the cerobrospinal fluid of narcoleptic patients [22]. Because orexins are believed to play a role in the maintenance of energy homoeostasis [25] these discoveries

provide a putative link between the disturbed regulation of the sleep-wake cycle and the clinical observation of increased obesity.

To further explore the relationship between narcolepsy and obesity we examined 132 patients with idiopathic narcolepsy, 52 first degree relatives of 22 of the patients and four monozygotic twin pairs for the occurrence of obesity.

Subjects

This study is part of a broader effort to clinically and genetically charcterize narcolepsy patients [18,6,10]. For the present analysis data from 132 narcoleptic patients (74 female, 58 male; mean age ± SD: 47.7 ± 16.6 years), including four monozygotic discordant twin pairs, were used. Of the 132 patients 129 reported cataplexies, the remainig three still fullfilled DSM criterion B (occurrence of either cataplexies or hallucinations or sleep paralysis). Of the patients 71 % were suffering from sleep paralysis, 78 % from sleep related hallucinations, and 86 % reported episodes of automatic behavior. Narcoleptic patients were either from the Department of Psychiatry, Mainz or recruited with the help of the Deutsche Narkolepsie-Gesellschaft, a nationwide German patients' organization. Most narcoleptic patients visited our department to participate in the narcolepsy research program; others who were unable or unwilling to come but eager to participate were visited by a member of the research team at home.

In addition 52 healthy (no narcolepsy) first degree relatives from 22 index patients, mostly from multiplex families, agreed to participate (29 female, 23 male; mean age ± SD: 42.1 ± 16.3 years). For additional control purposes, the BMI and age data from 104 (55 female, 49 male; mean age ± 43.9 ± 14.4 years) psychiatric inpatients (depression (n=41); alcohol dependence (n=17); schizophrenia (n=16); substance dependence (n=10); other (n=20) randomly chosen from a register of recent patients of the Department of Psychiatry, Mainz, were used. All participants gave written, informed consent. The study design was approved by the local ethics committee.

All patients fulfilled diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) [8] and the International Classification of Sleep Disease (ICDS) [20] of the American Sleep Disorders Association for narcolepsy.

Procedure

The narcoleptic patients had been diagnosed with narcolepsy either in the Department of Psychiatry, Mainz or in a certified sleep medicine unit elsewhere prior to the start of the study. Nine patients had not undergone polysomnography and Multiple Sleep Latency Test (MSLT) prior to the study; however they suffered from unambiguous cataplexies, additional REM symptoms and severe day time sleepiness. To exclude rare cases of symptomatic narcolepsy, the patients medical history was specifically assessed and a neurological check was performed.

The diagnostic reevaluation of the patients and the patients' relatives for the purpose of the study was performed through a clinical interview that included actual complaints or symptoms as well as medical, family and personal history. The interview was complemented by a symptom checklist that included all DSM criteria. In addition, medical records were obtained. All diagnoses were checked by an experienced physician (N. D.).

Assessments

For the structured assessment of symptoms, all patients and the patients' relatives filled out the Stanford Center for Narcolepsy Sleep Inventory, a 146 item questionnaire organized into nine sections. Section I and II report demographic information, section III includes the Epworth Sleepiness scale, section IV covers sleeping habits, section V–VIII contain items on cataplexy, hallucinations, sleep paralysis and automatic behavior, whereas section IX offers an opportunity to the patient to give remarks on items not already mentioned in the questionnaire. The cataplexy part of this questionaire has recently been published and validated in 983 sleep-disorders patients [2]. Body weight was measured using a calibrated electronic balance, in some cases (patients who were visited at home) self-reported interview data were used. Special consideration was given to the medication status of the patients, because many drugs used in the treatment of narcolepsy are known to exert effects on appetite and food intake in psychiatric patients as well as in healthy controls.

Data were compared to the results of recent German and Swiss population-based general surveys on eating and health, which included BMI and age data [9, 12–14]. Because the mean age of the narcoleptic patients was slightly higher than that of the relatives (p=0.04) and of the psychiatric controls (p=0.07) comparisons were made with the respective age group of the population surveys. In addition to mean data percentiles were used, because percentiles have been shown to be more informative in regard to diagnostic evaluation and can be more easily related to norm populations [13].

In the statistical comparisons of groups, two-sided unpaired t-tests were used. For the comparison of proportions, the Chi square test was used. Bonferroni adjustment of α error was applied where appropriate.

Results

The body mass indices (BMIs) of the narcoleptic patients were significantly increased in comparison to published population surveys as well as to the psychi-

Table 1 Comparison of mean body mass index ± standard deviation

	All	Women	Men
Narcoleptic patients (74 female, 58 male; mean age: 47.7 years)	28.2 ± 5.5	27.2 ± 5.8	29.5 ± 4.8
First degree relatives (29 female, 23 male mean age: 42.1 years)	25.3 ± 3.8** (p=0.0006; t=3.5)	25.1 ± 3.9 (p=0.08; t=1.8)	25.6 ± 3.6** (p=0.0007; t=3.5)
Psychiatric controls (55 female, 49 male mean age: 43.9 years)	24.5 ± 4.7*** (p < 0.0001; t=5.5)	24.4 ± 5.6 (p=0.007; t=2.7)	24.5 ± 3.3*** (p < 0.0001; t=6.2)
General population (1386 female, 1365 male (age group: 35–44 years)	23.5 ±3.5§§ (p=0.001; t=3.3)	22.4 ± 3.7§§ (p=0.0003; t=3.7)	24.6 ± 3.2 (p=0.16; t=1.4))
General population (1294 female, 1191 male age group: 45–54 years)	24.4 ± 3.7*** (p < 0.0001; t=8.0)	23.2 ± 3.9*** (p < 0.0001; t=4.6)	25.5 ± 3.4*** (p < 0.0001; t=7.4)

Symbols indicate statistical significance (three symbols: $p < 0.001$; two symbols: $p < 0.01$; two sided t-test, corrected for multiple testing). Asterisks: comparison with narcoleptic patients, §: comparison with first degree relatives. General population data are from ref. 9. Narcoleptic patients were compared to the age group 45–54 years and first degree relatives to the age group 35–44 years.

atric control group. First degree relatives' BMI was higher than the BMIs of the general population but lower than the BMIs of the narcoleptic patients (Table 1).

Whereas 25.4 % of the German [14] and 24.7 % of the Swiss [9] population are reported to be slightly obese (BMI 25–30), this number was 42 % for the narcoleptic patients, 43 % for first degree relatives and 27 % of the psychiatric controls. More strikingly, 5.5 % of the German and 5.2 % of the Swiss population are reported to be moderately to severely obese (BMI > 30), this figure was 32 % in the narcoleptic patients, 8 % for first degree relatives and 15 % in the psychiatric controls. When the data where analyzed in relation to the percentiles of BMI of the German National Nutrition Survey [12, 13], the dysproportional representation of particularly obese subjects among the narcoleptic patients became apparent. For example, roughly 18 % of the narcoleptic patients were beyond the 97 % BMI percentile of the German National Nutrition Survey (Fig. 1).

The increase of BMI was also seen in the comparison of affected and unaffected siblings (without twins). Here the mean BMIs were 29.6 ± 6.6 vs. 25.3 ± 2.9 (n=15, p=0.026; unpaired t-test). The relation between disease status and obesity was also apparent in the comparison of the four (discordant) monozygotic twins pairs among the patients. In two of the twin couples the narcoleptic twin had a higher BMI than the non-narcoleptic one, the BMIs were 24.9 vs. 20.3 and 30.5 vs. 26.6, respectively. However, additional factors were found in both cases that plausibly could have contributed toward the differences in BMI. In one case the affected twin had gained weight after being recovered from a stroke that had occurred years after the onset of narcoleptic symptoms; in the other case, the non-affected twin was suffering from a chronic colitis. In the two remaining twin couples the BMIs were essentially identical (21.6 vs 21.6 and 29.4 vs. 29).

On the day of the study 64.9 % of the patients were taking prescription drugs, 29 % amphetamines, 27.5 % antidepressants, 6.9 % sedatives and 47.3 % other prescription drugs. Of these classes of drugs, antidepressants are particularly relevant to the present study, because many antidepressants and virtually all tricyclic antidepressants show the side effect of increased body weight. However, the observed BMI increases could not be attributed to medication status. We dichotomized the patients into two groups, one with a tricyclic antidepressant therapy history of less than one month (-AD) and one group that had a positive lifetime history of tricyclic antidepressant medication of more than one month (+AD). Mean BMIs were not significantly diffe-

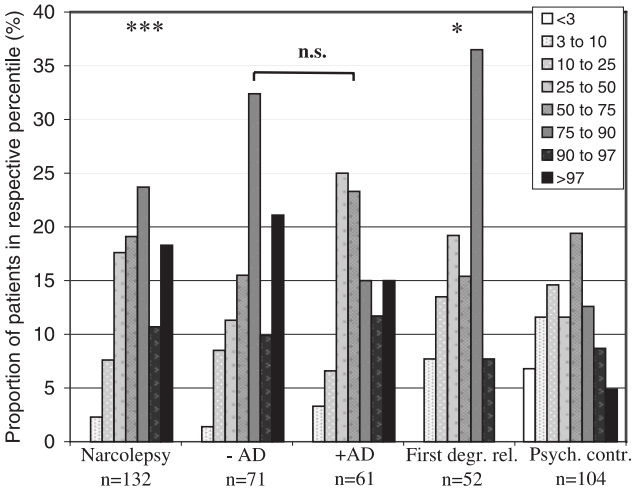

Fig. 1 Percent of patients within the percentiles of the German National Nutrition Survey. The proportion of patients above the 75th precentile is statistically increased in the narcoleptic patients and in the first degree relatives of the narcoleptic patients but not in the psychiatric controls in comparison with the controls of the German National Nutrition survey (Chi-squre test, two-sided). There was no significant difference between patients with a lifetime tricyclic medication of less than one month (-AD) and more than one month (+AD).

*** $p < 0.05$. Percentiles are derived from ref. 12.

* $p < 0.001$.

rent in either group: 27.9 ± 4.6 (+AD, n= 61) vs. 28.9 ± 6.1 (-AD, n= 71; n. s.) (Fig. 1).

Likewise, the BMI was unaffected by the severity of day time sleepiness, the frequency of cataplexies or the occurrence of the accessory symptoms hallucinations, sleep paralysis and automatic behavior. For this calculation, patients were dichotomized into a group of patients displaying the respective symptom rather predominantly and the other group that showed the symptom only to a lesser degree (in the case of cataplexies and day time sleepiness) or not at all (in the case of hallucinations, sleep paralysis and automatic behavior). BMIs were not significantly different between the respective groups.

Discussion

In our study we showed that narcolepsy patients are more obese than the average population. For example, roughly 18 % of the narcoleptic patients were beyond the 97 % BMI percentile of the German National Nutrition Survey [12, 13]. In this study 23 209 representative subjects from 11 141 independent households out of 24 632 subjects contacted between 1985 and 1989 reported anthropomorphic data for body height and weight. In a sub-study it was shown that self-reported data had been correctly within a 5 % error margin by over 80 % of the participants. The data of the German National nutrition survey are consistent with those reported in the Swiss National Health survey [9] from 1992/1993 in which 7358 women and 7930 men were contacted by phone and of additional surveys that were primarily aimed at general public health aspects [14], so that relating to the published data appeared not to be likely to generate unacceptable cohort effects or other biases. However, as an additional safeguard, the BMI data of the narcoleptic patients were also shown to be elevated in comparison to psychiatric inpatients that were used as an additional clinical control group.

The examination of 15 sibling pairs and of four discordant twin pairs revealed the same pattern of difference between the siblings or twins, respectively, although in two twin pairs other relevant factors apart from narcolepsy were observed, which plausibly could also have contributed to the BMI differences.

The data reported here confirm previous observations [15, 26] of increased body weight in narcoleptic patients. Therefore it is suggestive to view narcolepsy/obesity as a syndrome. This finding is of clinical importance, as many patients experience guilt and shame because of their increased body weight. The recognition of their weight problem as related to narcolepsy might help these patients cope psychologically, although it does not free anyone from the task to control body weight and food intake.

The increase of BMI was not due to the intake of antidepressive medication frequently administered to reduce REM-associated symptoms. This might be perceived as surprising; however, the doses of antidepressants needed in the treatment of narcolepsy are frequently rather small, e. g. 25–50 mg anafranil [11] and many patients only took antidepressants during limited periods of time, so that short-term weight gains might have been reversed.

The BMI increase appeared to be independent of symptom severity or the occurrence of the accessory symptoms hallucinations, sleep paralysis and automatic behavior. In addition, first degree relatives of patients were heavier than expected from general population surveys, but lighter than their narcoleptic relatives. Both observations could suggest that the increase of body weight is controlled in part by genetic factors, which are also relevant, albeit to a lesser degree, in a non-narcoleptic context.

From an behavioral view we can presently only offer anecdotal evidence towards possible explanations for the increased BMIs. Many patients reported atypical binge eating-like attacks that occur preferentially during night hours and periods of sleepiness. The combination of sleeping abnormalities and nocturnal hyperphagia has been described as "night eating syndrome" [28] and a better defined related if not overlapping syndrome has been labeled "sleep related eating disorder" [29]. The combination of behavioral desinhibition together with hypersomnia is known to occur in patients suffering from Kleine-Levin syndrome [19] another hypersomnic disorder with unknown etiology. Certainly, investigations of eating patterns of narcoleptic patients seem warranted. In addition, exploring the time relationship between narcolepsy symptom onset and obesity or changes in eating related behavior will be of interest.

The implication of the orexinergic system in the pathophysiology of narcolepsy [1, 27] is intriguing in the context of the increased BMI of narcoleptic patients. Orexins are believed to play a mediating role in the control of appetite and body weight. For example, injection of orexin 1 in the cerebrospinal fluids of animals leads to the initiation of feeding behavior [25]. However, this relation might be of a more complex nature since orexinergic neurotransmission may actually be reduced in narcoleptic patients [22, 24] and since genetic variants of known orexinergic genes might not play a major role in the majority of narcoleptic patients [21, 24].

In summary, our study confirms the association of narcolepsy and obesity and suggests that obesity may be an unspecific symptom of narcolepsy, although it can not completely be ruled out that obesity predisposes towards narcolepsy as this topic never has never been formally studied. Moreover, it points towards the existence of hitherto unknown genetic factors common to the obesity of narcoleptics and narcolepsy.

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References

1. Aldrich MS, Reynolds PR (1999) Narcolepsy and the hypocretin receptor 2 gene. Neuron 23:625–626
2. Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E (1999) Validation of a Cataplexy Questionaire in 983 Sleep-disorders patients. Sleep 22: 1, 77–87
3. Bundesverband der Deutschen Narkolepsie-Gesellschaft, Postfach 1107, 42 755 Haan, Germany
4. Cascardon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S (1986) Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 9:519–24
5. Chemelli MR, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98: 437–451
6. Dahmen N, Querings K, Grun B, Bierbrauer J (1999) Increased frequency of migraine in narcoleptic patients. Neurology 52: 1291–1293
7. Devlin MJ, Yanovski SZ, Wilson TG (2000) Obesity: what mental health professionals need to know. Am J Psy 157: 854–866
8. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC: American Psychiatric Association, 1994
9. Eichholzer M, Lüthy J, Gutzwiller F (1999) Epidemiology of overweight in Switzerland: results of the Swiss National Health Survey. Schweiz Med Wochenschr 129:353–361
10. Gencik M, Dahmen N, Wieczorek S, Kasten M, Bierbrauer J, Anghelescu I, Szegedi A, Menezes Saecker AM, Epplen JT (2001) A prepro-orexin gene polymorphism associated with narcolepsy. Neurology 56: 115–117
11. Guilleminault C (1994) Narcolepsy Syndrome. In: Kryger MH, Roth T, Dement WC (eds) Principles and Practice of Sleep Medicine. Philadelphia: W. B.Saunder Company, pp 594–561
12. Hebebrand J, Himmelmann G, Heseker H, et al (1994) Percentiles for the body mass index based on data of the German National Nutrition Survey and a review of relevant factors with an influence on body weight. Aktuelle Ernährungsmedizin 15:247–252
13. Hebebrand J, Himmelmann GW, Heseker H, Schafer H, Remschmidt H (1996) Use of percentiles for the body mass index in anorexia nervosa: diagnostic. Epidemiological and therapeutic considerations. Int J Eat Disord 19: 359–369
14. Hoffmeister H, Mensink GB, Stolzenberg H (1994) National trends in risk factors for cardiovascular disease in Germany. Prev Med 23:197–205
15. Honda Y, Doi Y, Ninomiya R, Ninomiya C (1986) Increased frequency of non-insulin-dependent diabetes mellitus among narcoleptic patients. Sleep 9: 254–259
16. Hublin C, Partinen M, Kaprio J, Koskenvuo M, Guilleminault C (1994) Epidemiology of Narcolepsy. Sleep 17: 7–13
17. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de-Jong PJ, Nishino S, Mignot E (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98: 365–376
18. Marx JJ, Urban PP, Hopf HC, Grun B, Dahmen N (1998) Electrophysiological brain stem investigations in idiopathic narcolepsy. J Neurol 245: 537–541
19. Mayer G, Leonhard E, Krieg J, Meier-Ewert K (1998) Endocrinological and polysomnographic findings in Kleine-Levin syndrome: no evidence for hypothalamic and circadian dysfunction. Sleep 21:278–284
20. MJ Thorpy (1990) ICDS – International classification of sleep disorders: Diagnostic and Coding Manual. Diagnostic Classification Steering Committee; Chairman, Rochester, MN, American Sleep disorders Association.
21. Nakayama J, Miura M, Honda M, Miki T, Honda Y, Arinami-T (2000) Linkage of human narcolepsy with HLA association to chromosome 4p13-q21. Genomics 2000;65:84–86
22. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E (2000) Hypocretin (Orexin) defiency in human narcolepsy. Lancet 355: 39–40
23. Partinen M, Hublin C, Kaprio J, Koskenvuo M, Guilleminault C (1994) Twin studies in narcolepsy. Sleep 17: 13–16
24. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, Nevsimalova S, Aldrich M, Reynolds D, Albin R, Li R, Hungs M, Pedrazzoli M, Padigaru M, Kucherlapati M, Fan J, Maki R, Lammers GJ, Bouras C, Kucherlapati R, Nishino S, Mignot E (2000) A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nature Medicine 6: 991–997
25. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behaviour. Cell 92: 573–585
26. Schuld A., Hebebrand J, Geller F, Pollmächer T (2000) Increased body-mass index in patients with narcolepsy. The Lancet 355: 1274–1275
27. Siegel JM (1999) Narcolepsy: a key role for hypocretins (orexins). Cell 98:409–412
28. Stunkard AJ, Grace WJ, Wolff HG (1955) The night eating syndrome. Am J Med 19: 78–86
29. Winkelmann JW (1998) Clinical and polysomnographic features of sleep related eating disorder. J Clin Psychiatry 59:14–19