

Eating Disorder and Metabolism in Narcoleptic Patients

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Study Objective: To evaluate eating behavior and energy balance as a cause of increased body mass index (BMI) in narcolepsy.

Design: Case controlled pilot study.

Settings: University hospital

Participants: 13 patients with narcolepsy (7 "typical" patients, with HLA DQB1*0602 and clear cut cataplexy, with suspected hypocretin deficiency; and 6 "atypical" narcoleptics, i.e., HLA negative or without cataplexy), and 9 healthy controls matched for age, gender, and ethnicity.

Intervention: Energy balance was evaluated by measuring BMI, rest energy expenditure with calorimetry, daily food and water intake, and plasma hormone levels. Eating behavior was evaluated using psychometric tests (EAT-40, EDI2, CIDI-2, MADRS).

Results: Patients with narcolepsy (whether typical or not) tended to be overweight and to have a lower basal metabolism than controls. Only patients with typical narcolepsy tended to eat less than controls. Narcoleptic patients who were overweight ate half as much as others, indicating

caloric restriction. Plasma glucose, cortisol, thyroid, and sex hormones levels did not differ between groups, while prolactin levels were twice as high in patients with narcolepsy as in controls. Narcoleptic patients had higher EAT-40 scores and more frequent features of bulimia nervosa (independent of depressive mood) than controls, suggesting a mild eating disorder, classified as "Eating Disorder Not Other Specified."

Discussion: Both lower basal metabolism and subtle changes in eating behavior (rather than in calorie intake) could explain the positive energy balance leading to overweight in narcolepsy. Eating behavior changes may be a strategy to control weight or to avoid daytime sleepiness.

Keywords: Narcolepsy, eating disorder, hypocretin, body mass index, metabolism

Citation: Chabas D; Foulon C; Gonzalez J; Nasr M; Lyon-Caen O; Willer JC; Derenne JP; Arnulf I. Eating disorder and metabolism in narcoleptic patients. *SLEEP* 2007;30(10):1267-1273.

INTRODUCTION

NARCOLEPSY IS A NEUROLOGICAL DISEASE AFFECTING 0.03%-0.1% OF THE GENERAL POPULATION IN WESTERN EUROPE AND NORTH AMERICA. THE disease primarily affects the generation of sleep. Most of the symptoms like excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations, are considered abnormal REM sleep intrusions during daytime. In addition to the sleep symptoms, several studies reported that some patients with narcolepsy could be obese. Daniels was the first to report, in 1934, that half of the patients would gain a substantial amount of weight (5-45 kg) around disease onset.¹ He observed that this phenotype was more frequent in women, in patients with abrupt onset, and in those with important somnolence since narcolepsy onset. Later, Kotagal reported that three quarters of children with narcolepsy onset before puberty were obese,² a finding confirmed by other

pediatricians.³ Compared to controls, narcoleptic children had higher body mass index (BMI), regardless of whether they were treated with drugs increasing appetite, and regardless of whether they had cataplexy.⁴ In addition, 5 of 31 patients had a history of binge eating. Narcoleptic adults have also higher BMI than the general population, as pointed by Schuld et al.⁵ Because obesity might be dependent on family genetics or habits rather than on narcolepsy, Dahmen and colleagues measured BMI in 129 Swiss and German patients with narcolepsy/cataplexy, and found that as many as a third of them were obese, compared to 8% of their first degree relatives and 5% of the general population.⁶ This high prevalence of obesity in narcolepsy was not confirmed in a larger sample of 485 American narcoleptics; the American narcoleptics had a marginal but significant increase (+1 kg/m²) of BMI compared to controls.⁷ Interestingly, the relative increase in BMI was more important in Asian than in Caucasian and Black narcoleptics, suggesting disease-ethnicity interaction. In summary, these results indicate that BMI may variably increase in patients with narcolepsy/cataplexy, and may be more prominent in childhood-onset narcolepsy and in patients submitted to specific genetic (e.g., Asian vs. Caucasian) and dietary background.

The interest for energy balance in narcolepsy has also increased since the discovery of hypocretin deficiency as the cause of canine,⁸ murine,^{9,10} and human^{11,12} narcolepsy/cataplexy. Hypocretin neurons are located in the lateral and perifornical hypothalamus and send projections throughout the brain, particularly to regions involved in sleep regulation and to the arcuate nucleus, a feeding center.¹³ Interestingly, hypocretins, also called orexins, were primarily known to influence feeding behavior and metabolism, as the central administration of orexin dose-dependently increases daytime food and water intake and metabolic rate.¹⁴ In addition, fasting upregulates the orexin synthesis, suggesting that these neurons sense the animal nutritional status and would acti-

Disclosure Statement

This was not an industry supported study. Dr. Gonzalez has received research support from Boehringer Ingelheim and Emphasys and has received equipment from Respirationics. Dr. Lyon-Caen has participated in speaking engagements for Biogen. Dr. Arnulf has received research support from Bioproject, Boehringer Ingelheim, and GlaxoSmithKline and has participated in a speaking engagement for UCB Pharma. Drs. Chabas, Foulon, Nasr, Willer, and Derenne have reported no financial conflicts of interest.

Submitted for publication July, 2006

Accepted for publication May, 2007

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vate arousal to search for food. This hypothesis is substantiated by the finding that prepro-orexin knockout mice and mice without orexin neurons (orexin/ataxin-3 transgenic mice) eat less.^{9,10} Since decreased food intake is not associated with weight loss in these animals, but with normal BMI⁹ or late onset obesity,¹⁰ the animals are suspected to have decreased metabolism.¹⁵ The transgenic mice are indeed hypoactive during the night (active) period.¹⁰ The current hypothesis is, therefore, that hypocretin deficiency decreases appetite and energy expenditure, but the latter more so, resulting in a positive weight gain.

How does this hypothesis apply in patients with narcolepsy? One may expect their BMI to increase when food intake exceeds energy expenditure. Whether narcoleptic patients eat more or less than controls is still a matter of debate. On one hand, early reports suggested that narcoleptic patients consume more carbohydrate rich food items than healthy subjects.^{16,17} A recent controlled study using food diary indicated that 22 patients with narcolepsy/cataplexy had a total kilojoule and carbohydrate consumption higher than controls.¹⁸ These patients initiated sweet consumption and snacking behavior more frequently than controls, but they did not consume more carbohydrate or kilojoules through snacks. Rather, they ate more food at meals. In contrast, Lammers reported that 12 narcoleptic patients ate significantly less (8.8±2.3 KJ/day) than controls (10.6±3.1 KJ/day), mainly because they ate less carbohydrates.¹⁹ It is, however, not indicated if patients and controls were matched for BMI. Although it is not mandatory associated with increased BMI, binge eating has also been reported in some narcoleptics.^{1,4} In addition, drugs used in narcolepsy/cataplexy have varied influences on BMI. Most stimulants decrease appetite,²⁰ while antidepressants active against cataplexy may increase appetite.²¹ All the above studies contrasted BMI in treated and untreated children and adults, and found no differences.

There has been, to our knowledge, no measure of energy expenditure in narcoleptic patients, and no ratio between calories intake and energy expenditure in narcolepsy. Eventually, the various hormones regulating the energy balance (thyroid stimulating hor-

mone, thyroxine, cortisol, prolactin) have rarely been measured systematically in human narcolepsy, except for decreased^{22,23} or normal²⁴ leptin levels, and for more frequent type II diabetes in narcoleptics.²⁵ We therefore conducted a pilot study measuring food intake, eating attitude, energy expenditure, and basal plasma levels of various hormones (but not leptin) in untreated patients with narcolepsy and in controls.

PATIENTS AND METHODS

Patients

Thirteen narcoleptic patients were randomly selected over 3 months from a cohort of approximately 500 patients with narcolepsy followed in the last 20 years in the outpatient clinic of the sleep department of the Pitié-Salpêtrière university hospital. They were matched for age, sex, and ethnicity with 9 healthy controls, recruited through advertisement (Table 1). The physical and neurological examination of the subjects was normal.

The diagnosis of primary narcolepsy was based on clinical signs (daily excessive daytime sleepiness for more than 3 months), overnight polysomnography (no other cause of daytime sleepiness), multiple daytime sleep latency (mean daytime sleep latency <8 minutes and ≥2 sleep onset REM periods), and HLA class II genotyping.²⁶ No patient had a family history of narcolepsy or concomitant neurological or psychiatric disease. As we did not measure cerebrospinal fluid hypocretin levels in our patients, we used the presence of clear-cut cataplexy and HLA positivity as a surrogate for hypocretin deficiency. Mignot et al. have shown on large samples that hypocretin deficiency (cerebrospinal hypocretin levels lower than 110 pg/ml) was observed in 100% of patients with frank cataplexy, HLA DQB1*0602 positivity, and no family history of narcolepsy or concomitant psychiatric or neurological disease.²⁷ Seven patients were HLA DQB1*0602 positive and had clear-cut cataplexy (typical narcolepsy). Six other patients with atypical narcolepsy suffer no (n=5, one with HLA positiv-

Table 1—Demographical and Clinical Characteristics of Narcoleptic Patients, With (Typical) or Without (Atypical) Clear-Cut Cataplexy and HLA Positivity, and Controls

	Narcoleptic patients		Controls
	Typical	Atypical	
Number of patients	7	6	9
Age (years)	22 (20-33)	30.5 (28-39)	29 (25-35)
Women	71%	67%	67%
Body mass index (Kg/m ²)	28.6 (21.9-29.1)	25.0 (22.9-26.1)	22.9 (20.5-23.6)
Subjects with overweight	4/7	3/6	1/9
Waist/hip ratio	0.90 (0.87-0.95)	0.82 (0.79-0.86)	0.77 (0.72-0.86)
Rectal temperature (°C)	36.7 (36.6-37)	37.0 (36.8-37.2)	36.7 (36.6-36.8)
Disease course (years)	6.0 (3.5-9.5)	5.5 (2.3-15.5)	-
Epworth sleepiness score	19 (15-20)	16 (14.3-17)	4.5 (2.7-11.2)**
Cataplexy	100%*	17%	0%
Hallucinations	86%	17%	0%
Sleep paralysis	43%	17%	25%
Mean sleep latency at MSLT (min)	2.9 ± 2.7	5.3 ± 3.3	-
Number of SOREMPs	4.2 ± 0.8	3.5 ± 1.0	-
HLA DQB1*0602 positive	100%*	17%	0%

*P<0.05 for a difference with atypical narcoleptics; **P<0.001 for a difference with narcoleptics. Body mass index tended to be higher in narcoleptics than in controls (P = 0.08). SOREMPs: sleep onset in REM periods; MSLT: multiple sleep latency test.

ity) or atypical cataplexy (n=1, HLA negative). Thus, it is likely that the typical patients with narcolepsy/cataplexy had hypocretin deficiency, while the atypical narcolepsy patients did not. Among narcoleptic patients, 6 had normal weight (BMI lower or equal to 25 kg/m²), and 7 were overweight (BMI greater than 25 kg/m²).

At the time of the study, all patients and controls were drug free for 2 months. Most narcoleptic patients were included in the study at the time of diagnosis, so that only 2 of them (15%) had been treated by modafinil for more than a week in the last 3 months, and 2 of them by fluoxetine (15%). One control (10%) had also been taking fluoxetine for the last 3 months. Finally, 2 narcoleptic patients (one in each group) were treated by levothyroxine for thyroid insufficiency (one as a late consequence of Hashimoto thyroiditis, one of unknown origin). Patients suffered from narcoleptic symptom for 11±13 years (range 1-47 years).

Sleep Interview

A sleep specialist performed a semi-structured sleep interview in all subjects (Table 1). It included the Epworth sleepiness score, the presence of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis, the duration of symptoms, and the frequency of cataplexy episodes.

Food Intake and Eating Behavior Evaluation

Patients and controls completed a daily food and water diary at home over a period of 3 consecutive days. A nutritionist evaluated the mean amount of calories and water ingested per day.

Eating behavior was evaluated by a trained psychologist using 3 psychometric tests: (1) the Composite International Diagnostic Interview (CIDI-2),²⁸ a face-to-face diagnostic test; (2) the Eating Attitude Test (EAT-40), an auto-questionnaire with scores ranging from 0 to 120²⁹; (3) and the Eating Disorder Inventory (EDI-2), an auto-questionnaire containing 11 primary symptom dimensions, including drive for thinness, bulimia, and body dissatisfaction.³⁰ Depression features were evaluated using the Montgomery and Asberg Depression Rating Scale (MADRS).³¹

Metabolism

Weight, height, BMI (weight/height²), waist and hip circumferences, waist/hip ratio, rectal temperature, heart rate and blood pressure were measured after an overnight fasting and a regular night sleep.

Resting energy expenditure was calculated from the results of indirect calorimetry and urinary nitrogen production,^{32,33} using a standard portable metabolic monitor (Deltatrac Metabolic Monitor, Datex Instrumentation Corp., Helsinki, Finland). The analyzers were calibrated before each study with air and precisely known gas concentration (96% oxygen and 4% carbon dioxide). This monitor has been validated for accuracy, sensitivity, and reproducibility over a wide range of conditions.^{34,35} Subjects were lying in bed in the morning, after an overnight fasting and a regular night sleep, under an airtight ventilated hood. They were instructed to rest quietly without sleeping for 30 minutes, while expired and inspired gases were continuously measured. Oxygen consumption was determined from the measurements of carbon dioxide and oxygen concentrations in the inspired and expired gases. A 10-minute metabolic steady state (lower than 5% change in the respiratory quotient) was required to retain a given measure.

Plasma Hormone Levels and HLA Genotyping

Blood samples were taken at 08:00 after overnight fasting, and plasma levels of thyroid stimulating hormone, free thyroxine (T₄), prolactin, follicle stimulating hormone, luteinizing hormone, cortisol, and glucose were measured. A high resolution HLA genotyping for DRB1 and DQB1 subtype was performed in all participants after extraction of DNA.

Statistical Analysis

All data are given as median (25th-75th percentiles). Group differences were analyzed with the Mann-Whitney U and chi-square tests. Correlations were estimated using Pearson coefficient. All reported P values are two-sided, with P < 0.05 as the significant threshold.

RESULTS

Body Mass Index and Vital Signs

Median BMI tended to be higher in the narcolepsy group (median: 25.8 kg/m²; 25th-75th percentiles: 22.5-28.9 kg/m²) than in the control group (22.9 kg/m²; 20.4-23.6 kg/m² P = 0.08). Seven of thirteen narcoleptics and 1/9 controls were overweight (P corrected=0.11). The BMI was however not different between typical and atypical narcoleptic patients, or between patients with and without recent (less than 3 years) onset narcolepsy (Table 1). There was

Table 2—Energy Balance in Patients With Narcolepsy and Controls

	Narcoleptic patients		All	Controls	P*
	Typical	Atypical			
Maximal weight, kg	80 (68-92)	77 (66-84)	80 (64-85)*	60 (57-69)	0.02
Minimal weight, kg	63 (52-70)	62 (57-73)	63 (55-75)	50 (49-52)	0.11
Max-min difference	17 (9-30)	12 (8-16)	14 (8-20)	10 (7-16)	0.38
Rest energy expenditure, kCal/kg/day	20.9 (19.4-22.7)	21.6 (20.7-23.1)	21.3 (19.7-23.1)	23.6 (20.9-25.5)	0.07
Food intake, kCal/kg/day	19.3 (17.7-23.7)	34.1 (27.3-38.9)	22.7 (17.7-34.9)	29.2 (25.4-36.1)	0.24
Water intake, ml/kg/day	31.8 (30.4-39)	39.3 (35.8-44.9)	34.9 (32-44.9)	35.9 (35.2-49.6)	0.35
Energy intake/expenditure	0.94 (0.87-1.18)	1.48 (1.14-1.68)	1.01 (0.86-1.48)	1.33 (1.08-1.52)	0.43

* P < 0.05, narcoleptics vs. controls

Table 3—Plasma Glucose and Hormones Levels in Narcoleptic Patients With (Typical) or Without (Atypical) Clear-cut Cataplexy and HLA Positivity, and Controls.

Plasma levels (norms)	Narcoleptic patients			Controls
	Typical	Atypical	All	
Free Thyroxine (T4) pmol/L (10-25)	13.4 (11.5-14.7)	14.7 (13.2-16.4)	13.9 (12.2-14.9)	15.0 (13.6-15.8)
Thyroid Stimulating Hormone mUI/L (0.1-4)	2.7 (1.9-3.8)	2.1 (1.6-2.3)	2.3 (1.7-3.2)	2.3 (1.8-2.7)
Prolactin ng/mL (1.7-27)	19.9 (16.9-22.3)	23.7 (12.6-29)	20.5 (14.8-28)	10.7 (7.4-15)*
Follicle Stimulating Hormone mUI/mL (2-13)	4.4 (1.9-11)	7.6 (4.8-9.2)	5.8 (3.3-10.3)	7.1 (5.5-8.8)
Luteinizing Hormone mUI/mL (1-11)	6.8 (3.6-10.4)	5.3 (4.4-8)	5.3 (4.1-9.9)	4.6 (3.6-7.1)
Cortisol 8 am ng/mL (6-30)	21.2 (19.5-24.2)	15.7 (12.2-20.1)	19.8 (13.5-22.6)	22.8 (21.8-23.7)
Glucose mmol/L(3.9-5.8)	4.7 (4.4-5.3)	4.6 (4.6-5.1)	4.7 (4.6-5.3)	4.7 (4.4-4.9)

*P < 0.05

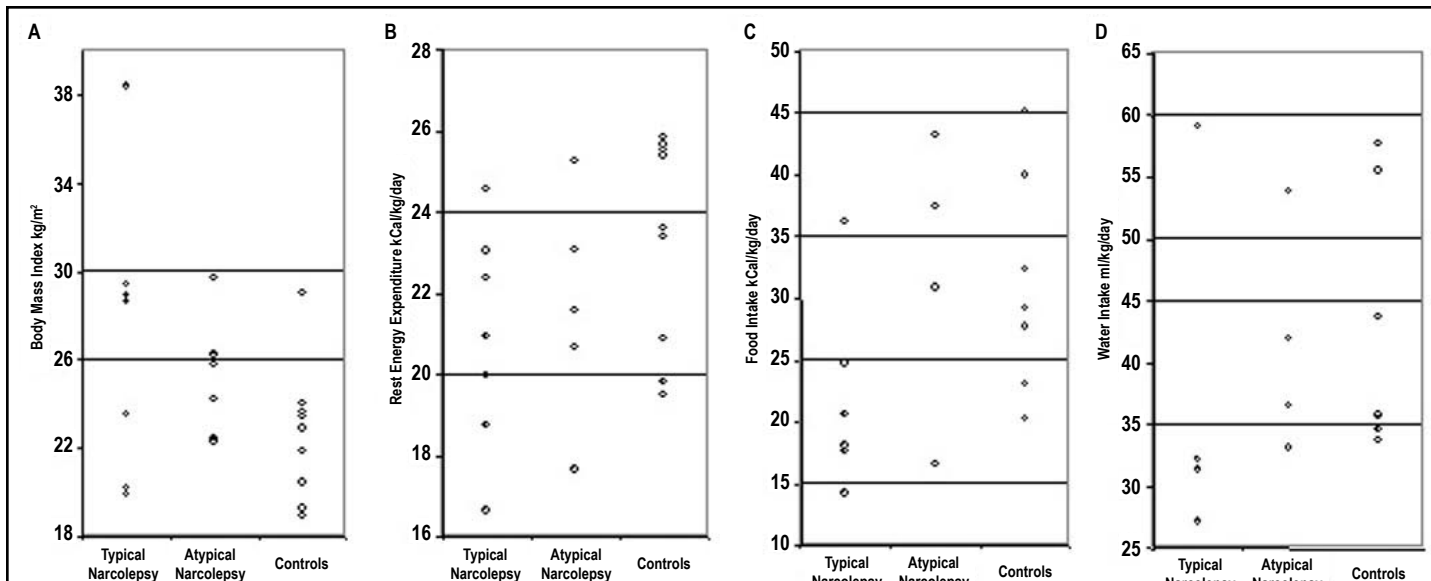


Figure 1—BMI (A), rest energy expenditure (B), food intake (C) and water intake (D) in narcoleptic patients (typical -HLA positive patients with cataplexy- and atypical) and controls. Overweight patients are represented with filled circles.

no difference in waist/hip ratio, heart rate, blood pressure, and rectal temperature between narcoleptic patients and controls, between typical and atypical narcoleptic patients, or between overweight and non-overweight patients (data not shown), except that systolic blood pressure was higher in overweight patients (120; 115-120 mm Hg) than in patients with a normal weight (110; 100-110 mm Hg, $P = 0.04$). In their past medical history, patients with narcolepsy had reached a higher maximal weight than controls, with no difference between typical and atypical narcoleptics (Table 2).

Energy Expenditure

Overall, narcoleptic patients tended to have lower rest energy expenditures than controls (Table 2). In the narcoleptic group, there was no difference in rest energy expenditure between typical and atypical patients. In contrast (Figure 1), overweight patients had significantly lower rest energy expenditure (20; 18.2-20.8 kCal/kg/day) than patients with normal BMI (23; 23-24.6 kCal/kg/day, $P = 0.004$). BMI correlated with rest energy expenditure in all subjects ($R = -0.80$, $P < 0.0001$), in the narcoleptic group ($R = -0.86$, $P < 0.0005$), with a similar trend in the control group ($R = -0.63$, $P < 0.07$), meaning that obese subjects, whether narcoleptic or not, had lower rest energy expenditure.

Food and Water Intake

Typical (but not atypical) narcoleptic patients tended to eat less than controls ($P = 0.06$, Table 2). They drank the same quantity of water per day than controls. There was no food or water intake difference between typical and atypical narcoleptic patients. Yet overweight narcoleptic patients ate half as much (17.6; 16.6-18 kCal/kg/day) as patients with a normal weight (36.2; 30.8-37.4 kCal/kg/day, $P = 0.009$) and had a lower daily water intake (31.8 vs. 47.9 ml/kg/day, $P = 0.02$). In order to determine if input exceeded output in the energy balance, we performed a ratio between energy intake and rest energy expenditure. This ratio was not different between narcoleptic patients and controls, or between typical and atypical patients. The ratio was however lower in overweight patients (0.86; 0.80-0.88, with intake being always lower than rest energy expenditures) than in patients with normal BMI (1.6; 1.4-1.7, $P = 0.03$).

Eating Behavior Disorder

Narcoleptic patients (Figure 2A) had twice higher EAT-40 scores (10; 9-19) than controls (4.5; 4-7.3, $P = 0.02$). In the narcoleptic group, the EAT score was not different between typical

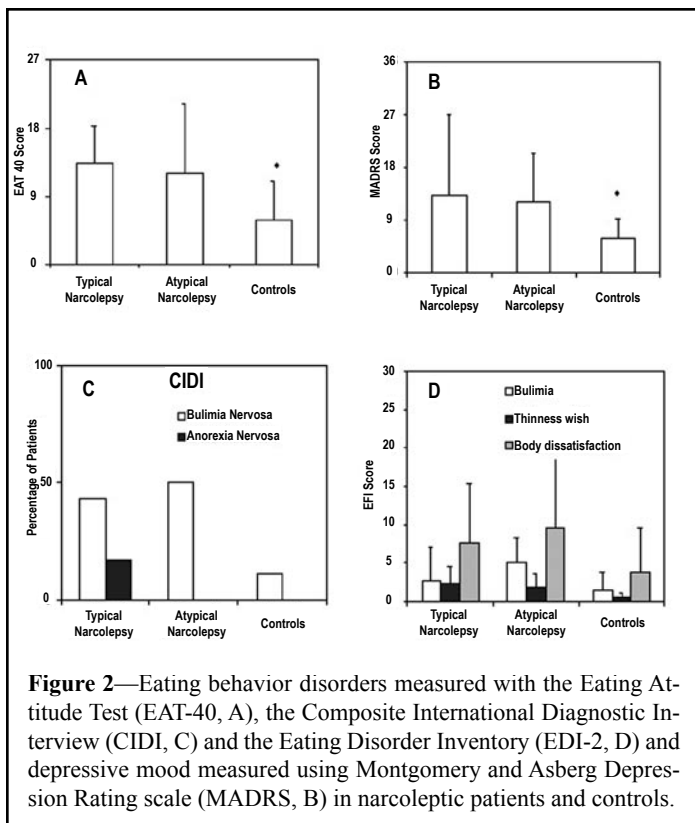


Figure 2—Eating behavior disorders measured with the Eating Attitude Test (EAT-40, A), the Composite International Diagnostic Interview (CIDI, C) and the Eating Disorder Inventory (EDI-2, D) and depressive mood measured using Montgomery and Asberg Depression Rating scale (MADRS, B) in narcoleptic patients and controls.

(10; 9-18) and atypical patients (14; 7-19, $P = 0.6$), nor between overweight patients (9; 4-19) and patients with a normal BMI (11; 9-19, $P = 0.7$). While there was a strong positive correlation between BMI and EAT-40 score in the controls ($R = 0.92$, $P = 0.0009$), this was not the case in the narcolepsy group ($R = 0.10$, $P = 0.78$). Using CIDI-2 (Figure 2C); 46% of narcoleptic patients were classified as having bulimia nervosa versus 11% in the control group ($P = 0.2$). Another narcoleptic patient was classified as having anorexia nervosa using the same test, making the percentage of narcoleptic patients having an abnormal CIDI-2 reaching up to 54% ($P = 0.11$, corrected chi-square). This trend for a pattern of bulimia or anorexia nervosa was equally observed in typical (43%) and atypical (50%) patients. Of interest, almost all (83%) narcoleptic patients with bulimia nervosa were overweight. Using EDI-2 subscales, narcoleptic patients tended also to score higher than controls for bulimia ($P = 0.14$), drive for thinness ($P = 0.15$) but not for body dissatisfaction ($P = 0.29$). There was no difference between typical and atypical narcoleptics (Figure 2D). When asked how they explain their eating attitude, several narcoleptic patients reported using food avoidance or binge eating as a way to manage daytime sleepiness. This included: (1) avoiding food at lunch to be more alert in the afternoon versus consuming high amount of food just before sleeping to reduce dyssomnia; (2) quickly eating snacks when feeling a sleep attack coming; (3) skipping lunch to nap during lunch time; (4) having irregular, unpredictable eating and sleeping schedules. As for depression, narcoleptic patients had higher MADRS scores (12; 10-18) than controls (6; 2-8, $P = 0.02$), with no further differences between typical and atypical narcoleptics, and between patients with normal or increased BMI (Figure 2B). The MADRS score did not correlate with the BMI, the EAT score, and the disease course.

Plasma Hormone Levels

Two patients treated with levothyroxine for thyroid insufficiency had normal plasma free thyroxine and thyroid stimulating hormone levels, while another untreated narcoleptic patient had abnormally high serum thyroid stimulating hormone levels (5.89 mIU/L, normal range: 0.1-4 mIU/L). It indicated a thyroid insufficiency in 3 of 13 (23%) narcoleptics, versus 0% controls ($P = 0.35$). As a mean, however, plasma thyroid stimulating hormone and free thyroxine levels were not different between narcoleptic patients and controls, and between typical and atypical narcolepsy (Table 3). Prolactin was twice as high in patients (with both typical and atypical narcolepsy) as in controls ($P: 0.03$). In addition, 4 patients with narcolepsy and one control had higher than normal serum prolactin levels. There was no significant difference regarding plasma cortisol, glucose, testosterone, follicle-stimulating hormone, and luteinizing hormone levels between groups.

DISCUSSION

Obesity is the result of a positive energy balance. In this pilot study, narcoleptic patients had a history of higher maximal weight than controls and tended to have higher BMI. In addition, they tended to have less rest energy expenditure than controls. Only narcoleptics with suspected hypocretin deficiency tended to eat less than controls. This suggests that hypocretin deficiency may decrease both basal metabolism and food intake in narcoleptic humans, as it does in a transgenic animal model of narcolepsy.¹⁰ Narcoleptics with overweight had lower food intake, compared to patients with normal weight and controls. This pattern is indicative of calorie restriction, a cognitive attitude and belief towards food and body shape repeatedly reported as a maintaining factor of obesity in adults. Decreased rest energy expenditure is also a classical consequence (not a cause) of increased proportion of body fat, while rest energy expenditure increases when muscles are developed.³⁶ However, as rest energy expenditure decreases with increased BMI in narcolepsy but not significantly in controls, it is probable that, in patients with narcolepsy, decreased energy metabolism is also a consequence of the disease itself, and not only of increased fat. The amount of muscle work, an important but variable component of energy balance, however, was not measured here. As narcoleptic patients need more daily sleep than controls and are more fatigued, they may be at risk of decreasing the quantity of daily exercise.

In addition to these trends in reduced basal metabolism and food intake, we found that half of narcoleptic patients suffered from a mild eating behavior disorder. This was confirmed both by standardized auto-questionnaire and face-to-face interview. Half of them had features of bulimia or anorexia nervosa. These results confirm a trend for binge eating already noticed by Daniels in some narcoleptic adults,¹ and by Kotagal et al in 16% of children with narcolepsy, even without overweight.⁴ When narcoleptic patients underwent further psychometric evaluation, all did not meet the precise diagnostic criteria of typical anorexia/bulimia nervosa.³⁷ Typical anorexia/bulimia nervosa usually affects adolescents and young adults, whose feeding behavior is driven by the desire for thinness. Moreover, typical anorexia/bulimia nervosa patients use weight control strategies like vomiting and laxatives to restore a normal weight after bingeing. While our narcoleptic patients with increased EAT scores were of all ages (18-

53 years, mean 30 years), drive for thinness, body dissatisfaction, and weight control strategies were not constant features. Thus, their eating disorder may be classified as atypical eating disorder or EDNOS (Eating Disorders not other specified), rather than typical anorexia/bulimia nervosa.³⁸ The prevalence of EDNOS in the general population is probably underestimated, and ranges from 5% to 14.6%, while bulimia nervosa affects around 1% to 2% of the population.³⁷ The intermediary EAT scores observed in narcoleptic patients, different from normal populations, were within the ranges observed in some subpopulations of subjects with EDNOS, including elite athletes, gymnasium users, top models and ballet dancers.³⁹⁻⁴¹ The physiopathology underlying bulimia nervosa and EDNOS is thought to be the same, since most atypical eating disorders closely resemble anorexia/bulimia nervosa. There is a genetic predisposition and a range of environmental risk factors participating in the physiopathology of the disease, although there is no unifying causal model. In narcoleptic patients, the eating disorder was more pronounced in overweight patients than in patients with normal weight, and most narcoleptic patients with bulimia nervosa were overweight, suggesting a direct relationship between eating disorder and overweight. Yet, food and water consumption was significantly lower in the overweight group at the time of the study, compared to narcoleptic patients with normal BMI and controls. It is possible that a qualitative change (eating less but more often, which is the case of most binges), rather than quantitative change (total of calories ingested), influenced body weight in these patients. Interestingly, in a previous study, narcoleptics ate more often than controls when placed in a 24-hr schedule (with more frequent snack after dinner), a difference that disappeared in free run condition.⁴² Our patients also reported that eating interfered with their alertness, whether as a stimulant or as a sedative, and that they modified food intake accordingly. As an example, in the study by Pollak and Green, narcoleptic patients were alert within 90 min before they chose to eat, but durably (150 min) sleepy after meals, whatever their nutrient content.⁴² Since narcoleptic patients with features of suspected hypocretin deficiency have eating disorders similar to atypical patients (except they tend to eat less), it suggests that the management of sleep-wake schedule, rather than hypocretin deficiency, influence the eating behavior in narcolepsy. Also, it is possible that dyssomnia, observed in one third of narcoleptic patients, contributes to weight increase as does sleep curtailment in healthy subjects.^{43,44} This point was not studied here.

There are several limitations to our study. First, we did not measure hypocretin levels in the CSF. Hypocretin deficiency was suspected from the typical narcolepsy profile (clear-cut cataplexy, HLA positivity, no familial history of narcolepsy, no other disease) of the patients, but not directly measured in the cerebrospinal fluid. From large series of patients, the risk for having no hypocretin deficiency in this group is however extremely low, while normal hypocretin function in atypical narcoleptics is more questionable.²⁷ We also did not measure in this study the leptin/ghrelin levels in the CSF and serum. We however recently measured leptin levels in the CSF and serum of a large group of patients with narcolepsy, and found no difference or correlation with hypocretin deficiency. Thus, we do not think that leptin plays an important role in the increased BMI of patients with narcolepsy.²⁴ The number of patients studied was small, leading to possible type I error, and to interesting trends that need to be confirmed in larger series. The small number of patients

did not allow us to study the influence of sex or disease course on the eating behavior. The sample contained two-thirds women while the usual ratio in narcolepsy is 1:1, possibly skewing the results towards more frequent eating disorders. Various case reports indicate that weight increase may be a feature of disease onset, possibly in children and teenagers. Here the patients with recent narcolepsy onset did not display a different BMI or energy balance than older patients, but no child or teenager was included in the study. All these limitations were balanced by the complete approach we used to study the causes of weight increase in our patients, using biometric and biological measures, food diary, and detailed analysis of eating attitude. We are however aware that food diary, filled out by patients themselves, are very subjective data, particularly in the context of anorexia/bulimia nervosa, and may underestimate the amount of calories ingested per day.

Eventually, patients with narcolepsy had increased plasma prolactin levels, an unexpected finding that needs to be replicated in larger groups before definitive conclusion. In animal models, hypocretin injections decrease serum prolactin levels, through hypocretin-1 receptors on prolactin cells.⁴⁵ Thus, one may imagine that decreased hypocretin in narcolepsy could increase prolactin levels.

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