Body Mass Index-Independent Metabolic Alterations in Narcolepsy with Cataplexy

Francesca Poli, MD[1]; Giuseppe Plazzi, MD[1]; Guido Di Dalmazi, MD[2]; Danilo Ribichini, MD[2]; Valentina Vicennati, MD[2]; Fabio Pizza, MD[1]; Emmanuel Mignot, MD[3]; Pasquale Montagna, MD[1]; Renato Pasquali, MD[2]; Uberto Pagotto, MD[2]

[1]Sleep Disorders Center, Department of Neurological Sciences, University of Bologna, Bologna, Italy; [2]Endocrinology Unit and Centro di Ricerca Biomedica Applicata (CRBA), Department of Clinical Medicine, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [3]Howard Hughes Medical Institute, Stanford University, Stanford, CA

Study Objectives: To contribute to the anthropometric and metabolic phenotyping of orexin-A–deficient narcoleptic patients, and to explore a possible risk of their developing a metabolic syndrome.

Design: We performed a cross-sectional study comparing metabolic alterations in patients with narcolepsy with cataplexy (NC) and patients with idiopathic hypersomnia without long sleep time.

Setting: University hospital.

Patients: Fourteen patients with narcolepsy with cataplexy and 14 sex and age-matched patients with idiopathic hypersomnia without long sleep time.

Interventions: N/A.

Measurements and results: Metabolic parameters were evaluated by measuring body mass index (BMI), waist circumference (also with abdominal computed tomography), blood pressure, and daily calorie intake (3-day diary). Chronotypes were assessed through the morningness-eveningness questionnaire. Lumbar puncture for cerebrospinal fluid orexin-A determination and HLA typing were performed. Patients with narcolepsy with cataplexy (all HLA DQB1*0602 positive and with cerebrospinal fluid orexin-A levels < 110 pg/mL) had a higher BMI and BMI-independent metabolic alterations, namely waist circumference, high-density lipoprotein cholesterol, and glucose/insulin ratio (an insulin resistance index), with respect to patients with idiopathic hypersomnia without long sleep time (cerebrospinal fluid orexin-A levels > 300 pg/mL). Despite lower daily food intake, patients with narcolepsy with cataplexy displayed significant alterations in metabolic parameters resulting in a diagnosis of metabolic syndrome in more than half the cases.

Conclusions: BMI-independent metabolic alterations and the relative hypophagia of patients with narcolepsy with cataplexy, as compared with patients with idiopathic hypersomnia without long sleep time, suggest that orexin-A influences the etiology of this phenotype. Moreover, considering that these dysmetabolic alterations are present from a young age, a careful metabolic follow-up of patients diagnosed with narcolepsy with cataplexy is mandatory.

Keywords: narcolepsy with cataplexy, orexin-A, metabolism, idiopathic hypersomnia, metabolic syndrome

Citation: Poli F; Plazzi G; Dalmazi GD; Ribichini D; Vicennati V; Pizza F; Mignot E; Montagna P; Pasquali R; Pagotto U. Body mass index-independent metabolic alterations in narcolepsy with cataplexy. *SLEEP* 2009;32(11):1491-1497.

NARCOLEPSY WITH CATAPLEXY (NC) IS A RARE SLEEP DISORDER CHARACTERIZED BY EXCESSIVE DAYTIME SLEEPINESS; CATAPLEXY (SUDDEN LOSS OF MUSCLE tone triggered by emotions); other abnormal rapid eye movement (REM) sleep phenomena, such as sleep paralysis and hypnagogic hallucinations; and disturbed nocturnal sleep.[1] Human NC is linked to a lack of orexin-A (also called hypocretin-1)–producing neurons[2,3] located in the posterolateral hypothalamus. Low or undetectable cerebrospinal fluid (CSF) orexin-A concentrations are highly specific and sensitive for human NC.[4-7] Orexin-A is not only involved in sleep regulation but also has been implicated in a number of behavior and neuroendocrine actions,[8,9] including the modulation of feeding behavior and energy balance.[10,11]

Accordingly, patients with NC display additional clinical symptoms besides REM-sleep abnormalities. Patients are often overweight or obese,[12,13] and many studies showing an increased body weight or body mass index (BMI) for patients with NC and an increased prevalence of type 2 diabetes in this population have been published in recent years.[14-20] An interesting association between the obese phenotype and a decreased food intake among narcoleptic subjects has also been reported.[21] Nevertheless, endeavors to explain this paradox through the peripheral role of other peptides and/or hormones (eg, leptin) have thus far failed to yield results.[22-24] There is no clear-cut evidence among NC subjects regarding the hypothesis of a lower energy rate or basal energy metabolism.[25,26] Lastly, several recent have attempted to relate the higher BMI to a feeding behavior disorder, with controversial results.[25,27,28] Thus, it can be inferred that, along with sleep-wake dysregulation, patients with NC often develop dysmetabolic phenotypes.

One aim of our study was to provide an exhaustive description of the anthropometric, metabolic, and food-behaviour phenotypes of drug-naïve patients with NC by comparing their metabolic profile with that of patients diagnosed with idiopathic hypersomnia without long sleep time (IH), another central hypersomnia, but one that is not related to a lack of orexin-A. A further aim of the study was to establish whether the metabolic alterations in patients with NC also meet the criteria for a diagnosis of metabolic syndrome.

Submitted for publication January, 2009
Submitted in final revised form May, 2009
Accepted for publication July, 2009
Address correspondence to: Giuseppe Plazzi, MD, Department of Neurological Sciences, Via Ugo Foscolo 7, 40123 Bologna, Italy; Tel: 39 051 2092926 50; Fax: 39 051 2092963; E-mail: giuseppe.plazzi@unibo.it

METHODS

General Study Design

A cross-sectional case-control study was performed comparing 14 NC with 14 patients with IH. The 2 groups were

sex and age matched; all patients were of Caucasian origin, in a postpubertal state, and drug naïve. The diagnoses were made according to the *International Classification of Sleep Disorders*, and brain magnetic resonance imaging studies were carried out to exclude hypersomnia due to other medical conditions.[1] Further exclusion criteria were brain lesions (confirmed by brain magnetic resonance imaging), psychiatric disorders,[29] clinical diagnosis of restless legs syndrome,[30] and polysomnographic diagnosis of obstructive sleep apnea syndrome. None of the patients had hyperprolactinemia, Cushing syndrome, congenital adrenal hyperplasia, thyroid dysfunction or other endocrine diseases, or cardiovascular, renal or liver diseases.

All subjects were recruited from consecutive patients referred for daytime sleepiness to the Sleep Disorders Center, Department of Neurological Sciences, University of Bologna, Italy. The study was approved by the local ethics committee. All patients gave their written informed consent before entry into the study.

Patients

NC Patients

Fourteen patients—diagnosed with NC—had excessive daytime sleepiness for at least 3 months, as assessed with an Epworth Sleepiness Scale pathologic score (i.e., ≥ 11).[31] Clear-cut cataplexy was clinically diagnosed by a neurologist with a structured interview focused on detailed descriptions of the attacks, their length, frequency, trigger factors, and parts of the body involved.[32] The presence of possible hypnagogic hallucinations and sleep paralysis was ascertained by history taking. Confirmation of instrumental diagnosis included continuous 48-hour polysomnography performed in a free-running condition, followed by a diagnostic multiple sleep latency test (MSLT), i.e., at least 2 sleep-onset REM periods and a mean sleep latency within 8 minutes.

IH Patients

Fourteen patients—diagnosed with IH—had excessive daytime sleepiness for at least 3 months assessed with an Epworth Sleepiness Scale pathologic score (i.e., ≥ 11). Confirmation of instrumental diagnosis included continuous 48-hour polysomnography, i.e., a nocturnal sleep lasting more than 6 and less than 10 hours during the baseline night (the night after the adaptation night) and a diagnostic MSLT, i.e., fewer than 2 sleep-onset REM-sleep episodes during MSLT and a mean sleep latency of 8 minutes or less.

Sleep Assessment

Two weeks before hospital admission, patients underwent night-sleep portable cardiorespiratory monitoring and filled out a restless legs syndrome questionnaire. Patients with an apnea-hypopnea oxygen desaturation index of 5 or more, a clinical diagnosis of restless legs syndrome,[30] or both an elevated index and a diagnosis of restless legs syndrome were not included.

The patients were also asked to keep a sleep diary for 1 week to assess subjective nocturnal sleep time and length, awake time, time and length of possible diurnal naps, and the morningness-eveningness questionnaire.[33] Patients with an altered circadian rhythm or cases at the extremities of the chronotype classification (namely extremely morning and extremely evening chronotypes) were excluded.

During their hospital stay, each patient was studied with continuous 48-hour polysomnogram, followed by a 5 nap-opportunity MSLTs. Polysomnography and MSLT were carried out after an adaptation night, in a standard sound-attenuated room, with continuous video-recording monitoring. The baseline night was considered the polysomnography recording after the adaptation night: lights-off time was based on individual habitual bedtime and ranged between 2130 and 2330; patients were allowed to sleep until they awoke spontaneously in the morning (i.e., free-running condition). MSLT was performed on the fourth day: the patient was awakened at 0730 and the 5 nap-opportunity tests started at 0930.[34]

During the 48-hour polysomnography recording, patients were allowed to sleep during the daytime whenever they wanted. They were not allowed to leave their rooms, except to go to the restroom, and were not allowed to drink caffeinated beverages. Three meals were eaten in the room at fixed times.

Cataplexy was identified according to its definition as sudden bilateral loss of muscle tone triggered by sudden emotions. In particular, the following restrictive diagnostic clinical criteria for cataplexy were used: (a) loss of muscle tone with the visible effect or involvement of other muscle groups in addition to legs, (b) duration of attacks shorter than 10 minutes, (c) preservation of consciousness, and (d) frequency of attacks (> 1 per week).[20]

Anthropometric, Biochemical, and Hormone Assessments

After the NC or IH diagnosis, each patient was also examined by the endocrinology team and had a complete clinical examination, focused on endocrine aspects. Height, weight, waist circumference (halfway between the lower rib and the crista iliaca), and hip circumference (the maximum value over the buttocks) were measured. BMI was evaluated according to the World Health Organization classification.[35] Waist-to-hip ratio was calculated according to standard procedures. Additionally, a measurement of body fat distribution using computed tomography was also performed between lumbar vertebrae L4 and L5 to estimate total, visceral, and subcutaneous adipose tissue areas. Clinostatic systolic and diastolic blood pressure and heart rate were measured. At home, a 3-day food diary was also kept by each patient. The daily energy intake; the type of single foods, condiments and sweeteners; and the macronutrient composition of the diet consumed in 3 consecutive days were evaluated.

Blood samples were collected after patients had fasted from midnight onward. Baseline blood samples were taken from an antecubital vein between 0700 and 0830 for biochemical and hormone determinations. The determinations included circulating concentrations of total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol; triglycerides; fasting plasma glucose; basal insulin; and leptin. An oral glucose tolerance test was also performed, with blood samples taken at baseline and 30, 60, 90, 120, and 180 minutes after the glucose load (75 gm) for glucose measurement and at baseline and 60, 120, and 180 minutes for insulin. All samples were immediately chilled on ice and centrifuged; serum or plasma aliquots

were frozen at -80°C until assayed. In addition, a blood sample was taken from each patient for HLA DQB1*0602 haplotype determination; patients also underwent a lumbar puncture for orexin-A CSF measurement after they sigend an additional informed consent form.

Assay

Plasma glucose levels were determined by the glucose-oxidase method. To measure peptide circulating levels, blood samples were collected in chilled Vacutainer tubes containing EDTA (1.8 mg/mL). The samples were centrifuged at 3000 rpm at 4°C, and the plasma collected was quickly frozen and stored at -80°C until assayed. Leptin was measured twice by direct assay on plasma using a specific commercial kit (Human Leptin RIA Kit, Linco Research, St. Charles, MO). Intraassay and interassay coefficients of leptin variations were 4.2% and 8.3%, respectively.

To investigate insulin sensitivity, the fasting glucose/insulin ratio (GLU/IRI), the quantitative insulin-sensitivity check index (QUICKI), and the homeostasis model assessment (HOMA) were calculated. The GLU/IRI ratio was calculated with glucose expressed as mg/dL and insulin as μU/mL. The HOMA-insulin resistance index (HOMA-IR) was calculated according to the formula: (fasting glucose (mmol/l] * fasting insulin (μU/mL] / 22.5).

CSF orexin-A was measured after solid phase extraction using a specific commercial kit (Human orexin-A RIA Kit, Phoenix Pharmaceutical, Inc., Belmont, CA). Before extraction, CSF samples (1 mL) were acidified with an equal amount of 1% trifluoracetic acid (TFA) in H_2O and then loaded on Sep Col C18, 200 mg (Phoenix Pharmaceuticals, Inc.) previously calibrated with 60% acetonitrile in 1% TFA. After washing with 1% TFA, the peptide was eluted with 60% acetonitrile in 1% TFA, collected, and evaporated under N_2. The residue was dissolved in RIA buffer and assayed. Intraassay and interassay variation coefficients for orexin-A were 5.2% and 9.1%, respectively.

Statistical Analysis

Data are reported as mean value ± standard deviation (SD), unless otherwise indicated. The responses of glucose and insulin to the oral glucose tolerance test were analyzed by calculating the area under the curve using the trapezoidal method. Simple correlation analysis was performed. A 1-way and multiple analyses of variance were applied to compare values among the groups and to evaluate the relationships between variables. Normal distribution of continuous variables was tested by means of the Kolmogorov-Smirnov test. Variables that were not normally distributed were logarithmically transformed before analysis. P values of less than 0.05 were regarded as statistically significant. Statistical analyses were performed by running the SPSS/PC (SPSS, Inc., Chicago, IL) software package. The daily energy intake and the composition of the diet in the 3-day diary were evaluated using Win Food Software, version 2.0.

Table 1—Demographic and Sleep Disorder-Related Characteristics

	Patients with NC	Patients with IH	P value
Men/women	14/0	14/0	-
Age, y	38.21 ± 13.71	33.29 ± 14.64	0.366
Duration of disease, y	16.64 ± 14.73	9.57 ± 7.50	0.122
Age at disease onset, y	21.57 ± 7.59	23.71 ± 12.99	0.599
Age at diagnosis of disease, y	30.07 ± 10.96	32.29 ± 14.89	0.658
Hypnagogic hallucinations	10 (71)	0 (0)	-
Sleep Paralysis	9 (64)	0 (0)	-
Cataplexy	14 (100)	0 (0)	-
Therapy	0 (0)	0 (0)	-
HLA DQB1 0602	14 (100)	1 (7)	-
CSF orexin-A, pg/mL	30.93 ± 27.44	348.30 ± 19.23	< 0.001
MEQ results			
Mild morning	4	4	-
Intermediate	6	6	-
Mild evening	4	4	-
ESS score	14.79 ± 4.627	13.00 ± 3.06	0.252
TST, min[b]	569.86 ± 97.67	522.29 ± 76.85	0.164
MSLT[c]			
Sleep latency, min	4.30 ± 3.65	6.35 ± 1.28	0.058
SOREMPs, no.	3.86 ± 1.23	0.29 ± 0.47	0.000003

Data are in mean ± standard deviation or number (%).NC refers to narcolepsy with cataplexy; IH, idiopathic hypersomnia; CSF, cerebrospinal fluid; MEQ, morningness-eveningness questionnaire; ESS, Epworth Sleepiness Scale.

[a]CSF samples were obtained from 14/14 patients with narcolepsy with cataplexy (NC) and 10/14 patients with idiopathic hypersomnia (IH).

[b]The total sleep time (TST) during 24-hour polysomnography was calculated taking into account the second part of the continuous 48-hour polysomnogram, ie, the baseline night and daytime naps of the following day.

[c]The Multiple Sleep Latency Test (MSLT) values of mean sleep latency and mean number of sleep-onset rapid eye movement periods (SOREMPs) were calculated on 5 nap opportunities.

RESULTS

Demographic and Sleep Disorder-related Characteristics

The demographic and sleep disorder-related characteristics of patients are shown in Table 1. The two sex- and age-matched groups showed similar duration of disease, age at onset, and age at diagnosis (P = 0.122; P = 0.599 and P = 0.658, respectively]. All patients displayed an intermediate or mild chronotype, as shown by the morningness-eveningness questionnaire. All 14 patients in the NC group carried the HLA DQB1*0602 haplotype versus 1 patient out of 14 in the IH group. CSF orexin-A levels were dramatically decreased in patients with NC (30.9 ± 27.4 pg/mL), whereas they were normal (348.3 ± 19.2 pg/mL) in the CSF of the patients with IH.[5]

The 2 groups did not show significant differences in sleep characteristics either in subjective sleepiness, assessed by the

Table 2—Anthropometric Parameters

	Patients with NC	Patients with IH	P value	P value[a]
No.	14	14		
Weight, kg	89.8 ± 16.2	76.6 ± 11.0	0.019	-
BMI, kg/m^2	28 ± 4.4	24.2 ± 2.8	0.012	-
Waist circumference, cm	102 ± 11	86 ± 8	< 0.001	0.001
Waist-to-hip ratio	0.95 ± 0.06	0.87 ± 0.04	0.003	NS
Adipose tissue, cm^2				
Total	67796.76 ± 18101.60	46311.15 ± 8666.90	0.004	NS
Subcutaneous	41104.15 ± 10342.59	27860.41 ± 6115.44	0.003	NS
Visceral	26692.61 ± 9692.18	18450.73 ± 3207.27	0.025	NS
Blood pressure, mm Hg				
Systolic	139 ± 16	128 ± 13	NS	NS
Diastolic	86 ± 11	78 ± 10	0.043	NS
Clinostatic heart rate, bpm	71 ± 8	71 ± 7	NS	NS

Data are presented as mean ± SD. NC refers to narcolepsy with cataplexy; IH, idiopathic hypersomnia.
[a]After body mass index (BMI) adjustment.

Table 3—Biochemical and Hormone Measurements

	Patients with NC	Patients with IH	P value	P value[a]
No.	14	14		
Cholesterol, mg/dL				
Total	201 ± 45	157 ± 37	0.016	NS
LDL	139 ± 46	102 ± 25	NS	NS
HDL	36 ± 11	52 ± 15	0.004	0.049
Triglycerides, mg/dL	179 ± 64	112 ± 57	0.008	NS
Glucose, mg/dL	80.4 ± 8.1	79.5 ± 12.4	NS	NS
Insulin, mcU/mL	11.3 ± 7.1	6.8 ± 3.3	0.047	NS
AUC glucose, mcU*mlL/min	22591 ± 4110	22399 ± 4661	NS	NS
AUC insulin, mcU*mL/min	15565 ± 12923	7519 ± 3031	0.040	NS
GLU/IRI	8.4 ± 2.9	13.2 ± 5.8	0.012	0.040
HOMA	2.2 ± 1.4	1.3 ± 0.5	0.034	NS
$HOMA_{OGTT}$	5.0 ± 2.4	7.5 ± 3.9	NS	NS
QUICKI	0.33 ± 0.05	0.39 ± 0.04	0.008	NS
Leptin, ng/mL	7.8 ± 4.2	3.9 ± 2.2	0.005	NS

Data are presented as mean ± SD. NC refers to narcolepsy with cataplexy; IH, idiopathic hypersomnia; AUC, area under the curve; GLU/IRI, glucose/insulin ratio; HDL, high-density lipoprotein; HOMA, Homeostasis Model Assessment; HOMA-IR, HOMA-Insulin Resistance Index; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; QUICKI, Quantitative Insulin-sensitivity Check Index.

ESS score (P = 0.252), or in polygraphic measured 24-hour total sleep time (i.e., the baseline night and daytime naps of the following day (P = 0.164). Mean sleep latency on MSLT did not show a significant difference (P = 0.058), whereas the mean occurrence of sleep REM periods during the 5 nap opportunities showed a significantly higher prevalence in patients with NC (P = 0.000003), as expected.

Anthropometric and Metabolic Parameters

Anthropometric parameters in the NC and IH groups are listed in Table 2. Weight and BMI were significantly higher in patients with NC (89.8 ± 16.2 kg and 28.0 ± 4.4 kg/m^2) compared with patients with IH (76.6 ± 11.0 kg and 24.2 ± 2.8 kg/m^2) (P = 0.019 and P = 0.012, respectively). Greater waist circumference (102 ± 11 vs 86 ± 8 cm) (P < 0.001) and waist-to-hip ratio (P = 0.003) were also detected in patients with NC, as compared with subjects with IH.

The computed tomography scan measurement of body fat distribution showed significantly higher areas of total adipose tissue, subcutaneous adipose tissue, and visceral adipose tissue in patients with NC, as compared with patients with IH (Table 2).

Diastolic blood pressure was significantly higher (86 ± 11 vs 78 ± 10 mm Hg) (P = 0.043) in patients with NC; higher systolic blood pressure, although not statistically significant, was also found in the same group (139 ± 16 vs 128 ± 13 mm Hg) (P = 0.075), whereas heart rate was comparable.

Patients with NC showed statistically significant reduced plasma levels of HDL cholesterol (36 ± 11 vs 52 ± 15 mg/dL) (P = 0.004) and higher total cholesterol (201 ± 45 vs 157 ± 37 mg/dL) (P = 0.016) and plasma triglycerides concentrations (179 ± 64 vs 112 ± 57 mg/dL) (P = 0.008) (Table 3).

Table 3 also shows subjects' values related to glucose tolerance and insulin resistance. Patients with NC had significantly higher fasting insulin (P < 0.047), insulin area under the curve values (P < 0.040), GLU/IRI ratio (P < 0.012), HOMA (P < 0.034), and QUICKI (P < 0.008), compared with the IH group. Leptin levels were also significantly higher in patients with NC, as compared with patients with IH (P < 0.008).

Given that patients with NC were significantly heavier than subjects with IH, statistical analyses between the 2 groups after adjusting for BMI were also performed (Tables 2 and 3). Patients with NC still showed a significant increase in waist circumference, in comparison with patients with IH (P = 0.001) (Table 2) and a statistically significant reduction of plasma HDL cholesterol (P = 0.049) and of GLU/IRI ratio (P = 0.040) (Table 3).

Dietary Habits

Patients with NC showed a statistically significant reduction of total daily caloric intake (1973 ± 401 Kcal), compared with IH cases (2341 ± 343 Kcal) (P = 0.027), evaluated through the total daily calorie intake of each patient (through self-administered 3-day food diaries) and the composition of the food. This difference remained significant also after BMI adjustment (P

Table 4—Metabolic Syndrome Parameters

NC patient	HDL, mg/dL	Triglycerides, mg/dL	Fasting glu, mg/dL	SBP, mm Hg	DBP, mm Hg	Waist circum, cm	Metabolic syndrome
1	54	71	69	124	81	96	no
2	**8**	**294**	73	**140**	**85**	**116**	yes
3	**31**	95	83	**150**	**95**	97	no
4	**38**	**163**	87	**135**	**85**	99	yes
5	45	**194**	78	112	68	**109**	no
6	**39**	**228**	83	**170**	**95**	**125**	yes
7	49	**182**	83	120	**85**	97	no
8	**32**	**206**	91	**145**	75	**102**	yes
9	**25**	**173**	83	**165**	**110**	94	yes
10	**30**	**172**	66	**140**	**85**	87	yes
11	**32**	N/A	79	**150**	**95**	**103**	yes
12	**36**	**159**	93	**130**	**85**	**104**	yes
13	**39**	**275**	87	**140**	**90**	**111**	yes
14	49	116	71	120	70	84	no
IH patient							
1	46	84	71	**140**	70	73	no
2	40	86	74	**130**	80	76	no
3	40	**162**	109	**130**	**90**	95	no
4	69	45	85	**140**	**90**	90	no
5	53	110	73	**140**	65	93	no
6	**37**	134	84	**130**	**85**	88	no
7	47	76	79	110	**86**	77	no
8	51	**171**	88	**150**	**85**	85	no
9	73	48	75	**135**	80	77	no
10	86	60	77	110	60	81	no
11	55	111	98	110	70	93	no
12	**38**	**191**	63	120	78	97	no
13	66	59	67	120	80	86	no
14	**34**	**226**	70	**130**	70	93	no

NC refers to narcolepsy with cataplexy; IH, idiopathic hypersomnia; HDL, high-density lipoprotein cholesterol; Fasting glu, Fasting glucose; Waist circum, Waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; N/A, not available. Pathologic values are bolded. The parameters for the diagnosis of metabolic syndrome were according to NCEP-ATPIII criteria.[36]

= 0.037). No alterations in the daily distribution of the macronutrients (lipids, carbohydrates, proteins) in the NC group and between groups were found.

Prevalence of Metabolic Syndrome

When the parameters for the diagnosis of metabolic syndrome were applied using NCEP-ATPIII criteria,[36] 9 out of 14 patients with NC (64.3%) displayed the metabolic syndrome. By contrast, none of the patients with IH were affected (Table 4).

When individual criteria of the metabolic syndrome in each subject were evaluated, 7 out of 14 patients with NC showed increased waist circumference, 10 showed low HDL cholesterol, and 10 high triglycerides; none showed abnormalities in fasting glucose, whereas 9 had hypertension. Among the patients with IH, none showed increased waist circumference, 3 had low HDL cholesterol, and 4 had high triglycerides; none showed abnormalities at fasting glucose, and 4 were hypertensive (Table 4).

DISCUSSION

This case-control study is the first to disclose an association between NC and BMI-independent metabolic alterations. After BMI adjustment, waist circumference, plasma HDL cholesterol, and GLU/IRI ratio were significantly altered in patients with NC. Moreover, our patients with NC had a higher prevalence of the metabolic syndrome.

Previous reports frequently showed an increased BMI in patients with NC[5,15-17,19] and a close association between NC and abdominal obesity.[18] Our findings extend these preliminary observations, emphasizing that several metabolic alterations are present in patients with NC, further suggesting a close association between NC and the metabolic syndrome. Compared

with patients with IH, patients with NC showed statistically significant increases in BMI, waist circumference, waist-to-hip ratio, and diastolic blood pressure. In addition, total and HDL cholesterol, triglycerides values, and many indexes of insulin resistance were pathologic in patients with NC. To rule out a possible pulling effect of the elevated BMI that we found in our patients with NC regarding the above metabolic alterations, we adjusted the statistical analysis for BMI and demonstrated that waist circumference, HDL cholesterol, and GLU/IRI ratio (index of insulin resistance) are pathologically altered in patients with NC, irrespective of BMI. Moreover, a large percentage of patients in the NC group (64%) had metabolic syndrome.

These data are even more interesting when the patients with NC-related hypophagia[21] is taken into account. Different from what one may expect in anthropometric measurements (namely BMI and waist circumference), patients with NC showed a significantly decreased food intake compared with patients with IH, thereby excluding the idea that altered food intake causes the dysmetabolism we noted. The dysmetabolism is independent of BMI, and BMI is inversely associated with food intake: these data support the notion that the lack of orexin-A may directly influence some metabolic parameters.[10]

We acknowledge some limitations in our paper. Our data do not definitively answer the question of whether the metabolic phenotype of patients with NC is at least partly due to a reduction in physical activity. To avoid this bias, we chose to compare a carefully age- and sex-matched NC and IH population, assuming that different central hypersomnias display a similar reduction and limitation in physical activity, as has been suggested by some quality-of-life surveys.[37-39] Our findings strikingly split the 2 groups in terms of prevalence of metabolic alterations, suggesting that altered mechanisms in basal metabolism affect patients with NC, but not subjects with IH. The finding that, overall, patients with NC showed a slightly lower rest energy expenditure[25] was not confirmed in a recent study, which reported a normal metabolic rate in BMI-matched patients with NC and control subjects.[26] A refined evaluation of 24-hour energy expenditure, coupled with accurate polysomnography monitoring—including autonomic parameters, could add further elements to explain whether the state of altered sleep control characterizing NC may reflect on metabolism.

A follow-up study could eventually show whether the insulin resistance (despite normal fasting glucose levels) that we found in our young patients with NC leads to a whole glucose metabolism impairment because we often observe type 2 diabetes mellitus among our elderly patients with NC.[14]

In conclusion, patients with NC showed BMI-independent metabolic alterations that, coupled with the animal data,[40] suggest a direct role of orexin-A in several metabolic processes. The relative hypophagia of patients with NC, together with their young age, further points to an intrinsic and peculiar metabolic alteration in NC.

Considering the chronicity of NC (for which an etiologic therapy is not yet available), the young age of onset of dysmetabolism (apparently not influenced by feeding habits), and the cardiovascular risk linked to the metabolic syndrome, our findings also suggest that a clinical and metabolic assessment should be performed when NC is diagnosed and throughout the life-long follow-up visits of patients with NC.

ACKNOWLEDGMENTS

We thank Dr. Rosaria de Iasio and Dr. Flaminia Fanelli for technical help, Dr. S. Vandi for neurophysiologic technical contribution, Dr. A.M. Morselli-Labate for statistical analysis, Ms. J. Coe and Ms. A. Collins for English revision, and Ms. A. Laffi for helping in manuscript editing.

Institution where work was performed: Department of Neurological Sciences, University of Bologna, Bologna, Italy

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

REFERENCES

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 2nd ed: Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine; 2005.
2. Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000;6:991-97.
3. Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000;27:469-74.
4. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000;355:39-40.
5. Nishino S, Ripley B, Overeem S, et al. Low cerebrospinal fluid hypocretin (orexin) and altered energy homeostasis in human narcolepsy. Ann Neurol 2001;50:381-8.
6. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553-62.
7. Dauvilliers Y, Baumann CR, Carlander B, et al. CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome, and other hypersomnias and neurological conditions. J Neurol Neurosurg Psychiatry 2003;74:1667-73.
8. Van den Pol AN, Gao XB, Obrietan K, Kilduff TS, Belousov AB. Presynaptic and postsynaptic actions and modulation of neuroendocrine neurons by a new hypothalamic peptide, hypocretin/orexin. J Neurosci 1998;18:7962-71.
9. Hagan JJ, Leslie RA, Patel S, et al. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci USA 1999;96:10911-6.
10. Willie JT, Chemelli RM, Sinton CM, Yanagisawa M. To eat or to sleep? Orexin in the regulation of feeding and wakefulness. Annu Rev Neurosci 2001;24:429-58.
11. Peyron C, Tighe DK, van den Pol AN, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 1998;18:9996-10015.
12. Cave H. Narcolepsy. Arch Neurol Psychiatr. 1931:50-101.
13. Daniels L. Narcolepsy. Medicine 1934;13:1-122.
14. Honda Y, Doi Y, Ninomiya R, Ninomiya C. Increased frequency of non-insulin-dependent diabetes mellitus among narcoleptic patients. Sleep 1986;9:254-9.
15. Schuld A, Hebebrand J, Geller F, Pollmächer T. Increased body-mass index in patients with narcolepsy. Lancet 2000;355:1274-5.
16. Dahmen N, Bierbrauer J, Kasten M. Increased prevalence of obesity in narcoleptic patients and relatives. Eur Arch Psychiatry Clin Neurosci 2001;251:85-89.
17. Schuld A, Beitinger PA, Dalal M, et al. Increased body mass index (BMI) in male narcoleptic patients, but not in HLA-DR2-positive healthy male volunteers. Sleep Med 2002;3:335-9.
18. Kok SW, Overeem S, Visscher TL, et al. Hypocretin deficiency in narcoleptic humans is associated with abdominal obesity. Obes Res 2003;11:1147-54.
19. Kotagal S, Krahn LE, Slocumb N. A putative link between childhood narcolepsy and obesity. Sleep Med 2004;5:147-50.
20. Serra L, Montagna P, Mignot E, Lugaresi E, Plazzi G. Cataplexy features in childhood narcolepsy. Mov Disord 2008;23:858-65.
21. Lammers GJ, Iestra J, Langius JAE, Buunk J, Meinders AE. Spontaneous food choice in narcolepsy. Sleep 1996;19:75-6.
22. Schuld A, Blum WF, Uhr M, et al. Reduced leptin levels in human narcolepsy. Neuroendocrinology 2000;72:195-8.

23. Kok SW, Meinders AE, Overeem S, et al. Reduction of plasma leptin levels and loss of its circadian rhythmicity in hypocretin (orexin)-deficient narcoleptic humans. J Clin Endocrinol Metab 2002;87:805-9.
24. Dahmen N, Engel A, Helfrich J, et al. Peripheral leptin levels in narcoleptic patients. Diabetes Technol Ther 2007;9:348-53.
25. Chabas D, Foulon C, Gonzalez J, et al. Eating disorder and metabolism in narcoleptic patients. Sleep 2007;30:1267-73.
26. Fronczek R, Overeem S, Reijntjes R, Lammers GJ, van Dijk JG, Pijl H. Increased heart rate variability but normal resting metabolic rate in hypocretin/orexin-deficient human narcolepsy. J Clin Sleep Med 2008;4:248-54.
27. Fortuyn HA, Swinkels S, Buitelaar J, et al. High prevalence of eating disorders in narcolepsy with cataplexy: a case-control study. Sleep 2008;31:335-41.
28. Dahmen N, Becht J, Engel A, Thommes M, Tonn P. Prevalence of eating disorders and eating attacks in narcolepsy. Neuropsychiatr Dis Treat 2008;4:257-61.
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Press, 2000.
30. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-19.
31. Vignatelli L, Plazzi G, Barbato A, et al. Italian version of the Epworth sleepiness scale: external validity. Neurol Sci 2003;23:295-300.
32. Anic-Labat S, Guilleminault C, Kraemer HC, et al. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. Sleep 1999;22:77-87.
33. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97-110.
34. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519-24.
35. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization, 2000.
36. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
37. Vignatelli L, D'Alessandro R, Mosconi P, et al. Health-related quality of life in Italian patients with narcolepsy: the SF-36 health survey. Sleep Med 2004;5:467-75.
38. Dodel R, Peter H, Spottke A, et al. Health-related quality of life in patients with narcolepsy. Sleep Med 2007;8:733-41.
39. Ozaki A, Inoue Y, Nakajima T, et al. Health-related quality of life among drug-naïve patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. J Clin Sleep Med 2008;4:572-8.
40. Hara J, Beuckmann CT, Nambu T, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. Neuron 2001;30:345-54.