Original Article

Body weight and basal metabolic rate in childhood narcolepsy: A longitudinal study

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ABSTRACT

Objective: The aim of this study was to document the trajectory of weight gain and body mass index (BMI) in children with type 1 narcolepsy, and to analyze basal metabolic rate (BMR).

Methods: A total of 65 Chinese children with type 1 narcolepsy with a disease duration ≤ 12 months were included. In addition, 79 healthy age-matched students were enrolled as controls. Height and body weight were measured every 6 months for up to 36 months to calculate BMI growth. BMR was measured using COSMED K4b2 indirect calorimetry in 34 patients and 30 healthy controls at 6 months. At the end of 36 months, the BMR was compared among 18 patients and 16 healthy controls.

Results: The children with type 1 narcolepsy showed higher BMIs at follow-up assessments. At the end of the study, 38.46% of the patients were obese and an additional 26.15% were overweight. The patients' BMI growth at 6, 12, 18, 24 and 30 months of follow-up was significantly higher, but not at month 36. The patients' basal energy expenditure was significantly lower than that of the controls at 6 months but not at 36 months.

Conclusion: BMI increased rapidly in children with type 1 narcolepsy after disease onset, but BMI growth decreased gradually with prolonged disease. Decreased BMR is an important cause underlying rapid weight gain. The gradual restoration of BMI growth and BMR in narcolepsy emphasizes the importance of compensatory metabolic mechanisms in this disease.

1. Introduction

Type 1 narcolepsy (also known as narcolepsy with cataplexy) is characterized by irrepressible daytime sleepiness attacks and emotion-evoked cataplexy [1]. Other prominent manifestations of this disease include nocturnal somniphobia, obesity, fatigue, sexual precocity, sleep apnea syndrome, and metabolic syndrome [2,3]. Globally, the disease peaks in adolescence [4,5], but it occurs mainly in children aged 8–12 years old in China [6,7] with a high incidence of obesity [8].

The primary pathophysiology of type 1 narcolepsy is characterized by serious deficiencies in hypocretin (Hcrt, also called Orexin)–secreting neurons in the lateral hypothalamus. In addition to controlling sleep/wakefulness, Hcrt also regulates metabolism, food intake, and the autonomous nervous system [9–11]. In addition to an extensive distribution in the brain [12], Hcrt and its receptors are expressed in peripheral tissues, such as the gastrointestinal tract, pancreas, and adrenal gland [13]. Hcrt regulates food intake, glucose metabolism, and fat metabolism via complex mechanisms [14]. Currently, it is believed that increased ingestion and reduced locomotor activities may cause the obesity in type 1 narcolepsy [15]. However, the precise cause of rapid weight gain in children with type 1 narcolepsy is still unclear.

To elucidate the features of body weight gain and metabolic features of narcolepsy, we performed a longitudinal study investigating body mass index (BMI) after onset of type 1 narcolepsy. We also monitored the trajectory of weight gain in children with type 1 narcolepsy. In addition, we adopted indirect calorimetry to investigate changes in basal metabolic rate (BMR) using before-and-after and case-control studies to explore the reasons for rapid weight gain after onset of narcolepsy.

2. Methods

2.1. Participants and protocols

This longitudinal case-control study was approved by the ethics committee of Changzheng Hospital, which is affiliated with the Second Military Medical University, Shanghai, China. The parents of all subjects signed informed consent, including 14 patients consenting for Hcrt testing from cerebrospinal fluid (CSF).

The study comprised two components, as detailed below.

2.1.1. Repeated BMI measurements

A total of 65 children (39 male and 26 female) who were diagnosed with type 1 narcolepsy using standard nocturnal polysomnography (PSG) and the Multiple Sleep Latency Test (MSLT) in the Neurology Department of Changzheng Hospital between January 2008 and March 2012 were selected. These patients were <15 years of age, with a mean age of 11.32 ± 3.68 years, and had a disease duration of ≤ 12 months. The control group consisted of 79 healthy students (41 male and 38 female), with matched ages, from a primary school in Shanghai, and a mean age of 11.53 ± 0.51 years. At enrollment, baseline heights and weights were measured, and then re-obtained every 6 months for up to 36 months to calculate BMI. To further analyze BMI changes over time in patients and controls, BMI growth was adopted. BMI growth (kg/m^2) is defined as the difference in BMIs measured before and after at two different time points, that is, BMI increase every 6 months. Data were collected from subjects and their parents by personal and/or telephone interviews and were analyzed by two of the authors (Z.W., H.W.). During the follow-up, the daily energy intake from diet was suggested at 30–35 (kcal/kg) by a hospital dietitian. Subjects performed almost identical levels of daily exercise to balance food intake and energy consumption during the study period. We guided patients to exercise 30 to 40 minutes a day, such as walking, jogging, swimming, cycling, table tennis, badminton, and other activities,

at least three times per week. From the interview recordings, most of the patients followed the above guidance. The medical history included sex, age, census, occupation, procreation status, parental health, chronic diseases, familial genetic history, and permanent residence.

According to ICSD-3 diagnostic criteria [1], the inclusion criteria included daily periods of irrepressible need to sleep or daytime lapses into sleep and cataplexy attacks induced by laughing/excitement for at least 3 months. A mean sleep latency of ≤ 8 minutes and two or more sleep onset rapid eye movement (REM) periods (SOREMPs) are found on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT. The exclusion criteria included the following: obstructive sleep apnea syndrome ($AHI > 10$ c/h), idiopathic hypersomnia or other sleep disorders, history of sleep restriction, shift work or jet lag, drug abuse (except medications to treat narcolepsy), or other neurological, psychiatric, or internal medicine diseases (such as diabetes or thyroid disease). Daytime sleepiness was evaluated in all subjects with the Epworth Sleepiness Scale (ESS), in which item 8 was deleted because of nonavailability.

2.1.2. Changes in BMR

A total of 34 patients (20 male and 14 female, mean age 11.36 ± 2.27 years) who participated in the BMI study with the consent of their parents also volunteered to participate in this study for 6 months of follow-up, including 14 patients who consented to testing for Hcrt-1 in CSF. A total of 30 healthy children (18 male and 12 female, mean age 11.92 ± 1.09 years) who were matched for age and sex volunteered to participate in this study, also with the consent of their parents. At the end of the study (36-month follow-up), 18 patients (11 male and 7 female, mean age 13.75 ± 2.14 years) at subsequent visit and 16 healthy controls (9 male and 7 female, mean

age 14.03 ± 0.98 years) underwent testing for BMR repeatedly. Sixteen patients did not participate at the second follow-up mainly because of living out-of-town, traffic burdens, difficulty being absent from school, or remission of symptoms of sleepiness or cataplexy. Based on the principles of voluntary trials, we could not require the patients to do anything against their will, and data from these subjects were omitted from subsequent analyses. A corresponding number of control subjects were also omitted from the analyses to preserve similar sample sizes between the two groups.

2.2. Basal metabolic rate

Metabolic indices were tested with indirect calorimetry using the Cosmed K4b2 portable metabolic measurement system (COSMED K4b2, Cosmed Co Ltd, Rome, Italy). Subjects fasted after 8 PM on the previous day. On the testing day, after fully waking up at 7 AM, subjects lay flat in a relaxed state and underwent testing for BMR according to the standard operational procedure. Each subject was tested for 15 minutes, during which time the room temperature was maintained at 22–24 °C, the humidity was 50–60%, and soft light (50–70 Lux) illumination was used. For 3 days before testing for BMR, individual daily energy intakes were maintained at 30–35 kcal/kg for each subject.

2.3. Body temperature

Patients underwent testing for rectal temperature using a mercury rectal thermometer (Shanghai Medical Instrument Factory, China). The mercury end was lubricated with paraffin wax and inserted about 5 cm into the anus. The temperature was read after 5 min and then again after another 5 min, to obtain an average value for the two trials.

2.4. Hcrt-1 content in CSF

The CSF was obtained using lumbar puncture in 14 patients, which was immediately stored at –80 °C in an ultra-low-temperature freezer and sent to Beijing

in liquid nitrogen. It was analyzed using an I¹²⁵ radioimmunoassay kit (Phoenix Pharmaceuticals, USA) by one of the authors (F.H.) and Dr. Li (Beijing People's Hospital), with standard CSF samples containing known Hcrt-1 levels obtained from Stanford Center for Narcolepsy [19].

2.5. Statistical analysis

A database was established using EpiData 3.0 software, and statistical analyses were performed using SPSS 19.0 software. Continuous variables were expressed as means and standard deviations, and categorical variables were described as median and extreme values. Group comparisons of normally distributed variables, non-normally distributed variables, and count data were performed using *t* tests, rank sum tests, and χ^2 tests, respectively. Within-subject comparisons were assessed using paired-sample *t* tests or Wilcoxon signed rank tests. BMI changes were analyzed using repeated-measurements and analyses of variance. Sphericity tests were performed to identify correlations between repeated measurements. The roles of time and grouping factors and the interactions between time and grouping were analyzed. Subsequently, multiple comparisons of BMI increases at different time points between the patient and control groups were performed using analysis of covariance. The changes at 6-month follow-up were considered baseline data for one-way analysis of variance. All *p* values presented are two-tailed. A value of *p* < 0.05 was considered statistically significant.

3. Results

3.1. Trends in BMI and BMI growth during 36-month follow-up

Multiple Sleep Latency Test results were obtained for all patients (mean MSLT of 2.04 ± 0.53 minutes with 3.56 ± 0.61 SOREMPs). The mean EDS score of the patient

group was 14.43 ± 2.87 . The subjects' demographic and diagnostic results are listed in Table 1, which show statistically nonsignificant differences in age and sex between the two groups.

The average BMI of the patient group was $20.60 \pm 3.13 \text{ kg/m}^2$ at the first interview. Based on the BMI reference norm for screening overweight and obesity in Chinese children and adolescents [20], 11 patients were classified as overweight (16.92 %) and 9 patients were classified as obese (13.85 %). At the end of the study (ie, at the 36-month follow-up), the average BMI was $23.59 \pm 3.13 \text{ kg/m}^2$. Body weight increased significantly in 42 patients (64.62 %), including 17 who were overweight (26.15 %) and 25 who were obese (38.46 %), which was significantly higher than in the control group ($p < 0.001$) (Table 1).

The average BMI of the control group was $16.25 \pm 2.84 \text{ kg/m}^2$ when included in the study. Four controls were classified as overweight (5.06 %), and 2 controls were classified as obese (2.53 %). At the end of the study, the average BMI was $18.18 \pm 2.82 \text{ kg/m}^2$; 4 controls were overweight (5.06 %) and 3 controls were obese (3.80 %), of whom 1 individual (1.27%) was clinically diagnosed with physiological obesity (Table 1).

Table 1

Clinical demographics and anthropometric data of study participants

Variable	Patients ($n = 65$)	Controls ($n = 79$)	p
Age (y)	11.32 ± 3.68	11.53 ± 0.51	0.984
Sex (male:female)	39:26	41:38	0.403
ESS (seven-item)	14.43 ± 2.87	3.51 ± 0.64	< 0.001
MSLT-sl (min)	2.04 ± 0.53	13.42 ± 2.17	< 0.001
SOREMPs	3.56 ± 0.61	0.15 ± 0.26	< 0.001
Disease duration (mo)	8.67 (3.5-12)	—	—

EWG, ^a n (%)	20 (30.77 %)	6 (7.59 %)	0.021
Overweight, ^a n (%)	11 (16.92 %)	4 (5.06 %)	0.020
Obesity, ^a n (%)	9 (13.85 %)	2 (2.53 %)	0.023
EWG, ^b n (%)	42 (64.62 %)	7 (8.86 %)	< 0.001
Overweight, ^b n (%)	17 (26.15 %)	4 (5.06 %)	0.002
Obese, ^b n (%)	25 (38.46 %)	3 (3.80 %)	< 0.001

ESS, Epworth Sleepiness Scale; EWG, excessive weight gain; MSLT, Multiple Sleep Latency Test; -sl, sleep latency; SOREMPs, sleep onset rapid eye movement periods.

^aAt the time of study inclusion.

^bAt the end of the study.

BMI values in the patient group increased suddenly from the first year of the disease and continued to increase with prolonged disease duration up to the 36-month interview. BMI values in the control group were consistent with the trend of gradual increase in Chinese children and adolescents younger than 18 years, as shown in Fig 1a.

The sphericity test results were significant ($p < 0.001$), which indicated that the repeated measurements were highly correlated. The repeated-measures analysis of variance demonstrated that time, group, and the time $\times$ group interaction were statistically significant ($p < 0.01$), whereas the effect of time varied by group. These results showed that BMI in the patient group increased gradually during the 36 months of follow-up.

The BMI growth in the patient group was significantly higher than that in the control group from 6 months to 30 months. At 36 months of follow-up, the difference was not statistically significant (Fig. 1b).

Body height showed a tendency to increase in both groups. No significant difference was observed in body height growth (kg) between the patient group and the control group ($p > 0.05$). Body weight growth (cm) also showed a tendency to

increase in both groups, but the weight growth in the patient group was higher than that in control group ($p < 0.01$) (Fig. 1c and 1d).

(a) BMI changes from baseline to 36 months.

(b) BMI growth every 6 months.

(c) Body height growth every 6 months.

(d) Body weight growth every 6 months.

Fig. 1. Body mass index (BMI), height, and weight changes in the study participants.

BMI growth in the patient group (■) at 6 months, 12 months, 18 months, 24 months, and 30 months of follow-up were significantly higher than in the control group (●) ($p < 0.01$). At 36 months, BMI growth in the patient group was not significantly different compared with that in the control group ($p = 0.21$). Repeated-measures analysis of variance revealed that BMI growth gradually decreased over time. No significant difference was observed in body height growth between the patient group

and the control group ($p > 0.05$). Body weight growth in the patient group was higher than that in the control group ($p < 0.01$).

3.2. Changes in BMR

In the 34 children (20 male and 14 female) in the patient group with type 1 narcolepsy, the mean age was 11.36 ± 2.27 years, and the disease duration was 15.4 months (range, 9–24 months). Of the patients, 14 underwent testing for Hcrt-1 content in the CSF (28.05 ± 24.50 ng/L). The mean age of the 30 healthy children (18 male and 12 female) in the control group was 11.92 ± 1.09 years. Differences in demographic characteristics between the patient and control groups were statistically nonsignificant. Cosmed k4b2 data revealed that the EEkc (kcal/day), EEkg (kcal/kg/day), and metabolic equivalents (METs) in the patient group were significantly lower (~25%) than in the control group (EEkc 1366.34 ± 294.37 vs 1823.89 ± 301.54 kcal/day, $p = 0.007$; EEkg 31.05 ± 6.19 vs 43.43 ± 7.28 kcal/kg/day, $p = 0.016$, METs 1.54 ± 0.41 vs 1.71 ± 0.35 , $p = 0.024$, respectively). However, the difference in the rectal temperature between the two groups was not statistically significant (36.72 ± 0.22 vs 36.87 ± 0.28 , $p = 0.691$) (Table 2).

At the end of the study (36 months), the BMR and the rectal temperature were re-tested in 18 patients. Under these conditions, the differences in demographic characteristics between the patient and control groups were statistically nonsignificant. Cosmed k4b2 measurements revealed that the EEkc (kcal/day), EEkg (kcal/kg/day), and METs in the patient group did not show significant differences compared with those in the control group (EEkc 1696.13 ± 416.77 vs 1800.75 ± 336.64 kcal/day, $p = 0.251$; EEkg 39.90 ± 8.61 vs 42.47 ± 11.91 kcal/kg/day, $p = 0.463$; METs 1.62 ± 0.39 vs 1.70 ± 0.51 , $p = 0.146$).

Within-patient comparison of BMR data for the group of patients showed the EEkc (kcal/day) and EEkg (kcal/kg/day) at 36-month follow-up were obviously higher than those at 6-month follow-up (EEkc 1366.34 ± 294.37 vs 1696.13 ± 416.77 kcal/day, $p < 0.001$; EEkg 31.05 ± 6.19 vs 39.90 ± 8.61 kcal/kg/day, $p < 0.001$;). METs in the patient group did not show significant differences (METs 1.54 ± 0.41 vs 1.62 ± 0.39 , $p = 0.080$). However, in the control group, within-subject comparison of EEkc (kcal/day), EEkg (kcal/kg/day), and METs did not show significant differences (EEkc 1823.89 ± 301.54 vs 1800.75 ± 336.64 kcal/day, $p = 0.780$; EEkg 43.43 ± 7.28 vs 42.47 ± 11.91 kcal/kg/day, $p = 0.393$, METs 1.71 ± 0.35 vs 1.70 ± 0.51 , $p = 0.944$).

Furthermore, the difference in the rectal temperature between the two groups was not statistically significant (36.74 ± 0.23 vs 36.81 ± 0.24 , $p = 0.759$).

Table 2

Cosmed K4b2 analysis of study participants

Variable	6-Month follow-up		36-Month follow-up	
	Patients ($n = 34$)	Controls ($n = 30$)	Patients ($n = 18$)	Controls
Age (y)	11.36 ± 2.27	11.92 ± 1.09	13.75 ± 2.14	14.03 ± 2.14
Sex (male:female)	20:14	18:12	11:7	9:7
Disease duration (mo)	15.4 (9–24)	—	41.4 (39–48)	—
ESS score	$14.41 \pm 3.32^{**}$	4.13 ± 1.69	$11.26 \pm 2.15^{**}$	3.18 ± 1.12
Rectal temperature (°C)	36.72 ± 0.22	36.87 ± 0.28	36.74 ± 0.23	36.81 ± 0.24
BSA (m ²)	$1.32 \pm 0.23^*$	1.27 ± 0.21	$1.44 \pm 0.32^*$	1.36 ± 0.23
BMI (kg/m ²)	$20.34 \pm 2.82^{**}$	17.51 ± 2.01	$23.05 \pm 3.12^{**}$	18.26 ± 2.14
RQ	0.79 ± 0.07	0.83 ± 0.09	0.83 ± 0.06	0.84 ± 0.06
HR (beats/min)	79.26 ± 10.03	83.38 ± 11.56	78.34 ± 11.46	82.51 ± 11.46
EEkc (kcal/day)	$1366.34 \pm 294.37^{**}$	1823.89 ± 301.54	1696.13 ± 416.77	1800.75 ± 336.64
EEkg (kcal/kg/day)	$31.05 \pm 6.19^*$	43.43 ± 7.28	39.90 ± 8.61	42.47 ± 11.91

METS	1.54 ± 0.41*	1.71 ± 0.35	1.62 ± 0.39	1.70 ± 0
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BMI, body mass index; BSA, body surface area; Cosmed K4b2, portable metabolic measurement system; EE, energy expenditure; ESS, Epworth Sleepiness Scale; HR, heart rate; METs, metabolic equivalents; RQ, respiratory quotient.

* $p < 0.05$.

** $p < 0.01$.

4. Discussion

4.1. Rapid weight gain after disease onset

In this study, for the first time, we document the trajectory of weight gain and BMI in children with type 1 narcolepsy from the early stage to 3–4 years later. Our findings showed that body weight and BMI of patients in an early stage of narcolepsy were significantly higher than those in their healthy peers. The numbers of patients classified as overweight or obese increased over the course of the study. BMI was significantly increased, with 64.62% of patients showing significantly increased body weight at 3–4 years after onset (overweight, 26.2%; obese, 38.5%). In the physical developmental period of healthy children and adolescents, body weight significantly increases with increasing age [20]. However, weight gain in children with type 1 narcolepsy dramatically exceeded the normal physiological growth.

It has been reported in many studies that the incidence of overweight or obesity ranges from 25% to as high as 74% in patients with type 1 narcolepsy [8,21,22]. However, the reliability of these rates has been questioned by the confounding effects of patients' age, sex, and disease duration. To address these sources of variability, this study enrolled children with type 1 narcolepsy with a disease duration of ≤ 12 months and compared them to healthy peers. Animal studies have also indicated that body weight gain in adult mice with silenced hypothalamus *Hcrt* gene (observation

duration 4–20 months) was continuously higher than in the wild-type mice [23]. Since the patients were under controlled energy intake and exercise conditions during the follow-ups, such a pathologic weight gain leads to a remarkably increased incidence of obesity/overweight, and suggests the presence of significant metabolic disorders in patients.

4.2. Changes in BMI growth

We then found that the BMI growth was significantly elevated in patients with early-stage type 1 narcolepsy. BMI gradually decreased with prolonged disease duration, and was restored to a level similar to that in healthy peers at 3–4 years after disease onset. These findings suggest that episodic increases in body weight occur during type 1 narcolepsy. Controlling for diet and exercise, the findings in our study suggest that the sudden increases in BMI growth in the early stage of disease are related to altered basal energy metabolism.

Although obesity or excessive weight in patients with narcolepsy is very common, previous studies have mostly focused on observation and description of clinical manifestations, rather than trends over time. Because of increased growth in children and adolescents, changes in BMI alone do not reflect its metabolic characteristics [24]. Nevertheless, BMI growth facilitates the analysis of dynamic metabolic changes in children and adolescents [25]. Therefore, the gradual restoration of BMI growth to normal levels may predict metabolic recovery in narcolepsy.

4.3. Changes in BMR

Energy intake that is higher than energy consumption leads to fat accumulation and obesity [26]. Increased diet and/or decreased exercise boost energy levels and/or decrease energy consumption, leading to obesity [27]. Body weight may differ remarkably in individuals due to different BMR, even with similar energy intake and exercise [26]. A number of studies have reported conflicting results about the role of

BMR in narcolepsy-related obesity. A few studies found that resting energy expenditure was reduced in patients with narcolepsy [17,28]. However, other studies demonstrated that the BMR did not significantly differ between patients and healthy controls [16,18]. These inconsistent results may be related to the small sample size in these studies, or to differences in patients' ages or disease durations. Therefore, in this study, we controlled the factors of disease duration and age to improve the test protocol. We found that for type 1 narcolepsy lasting 9–18 months, the BMR (morning, fasting, waking, resting, and lying flat) was reduced by about 25% compared with that in normal peers. BMR was also restored to a healthy level after 3.5 to 4 years. These results were consistent with the regression trajectory of BMI growth.

The mechanism of *Hcrt* regulation of metabolism is highly paradoxical. Experimental studies have reported that *Hcrt* stimulated appetite via neuropeptide Y. Thus, *Hcrt* deficiency leads to appetite loss and hypophagia [29]. Molecular studies revealed that *Hcrt* significantly regulates fat metabolism by promoting fat accumulation via reduced lipolysis [30,31]. Therefore, *Hcrt* deficiency should result in increased lipolysis and reduced body weight [32]. However, conversely, clinical and animal models of narcolepsy showed fat accumulation and significantly increased body weight after onset [23,33–35]. An explanation for this paradox may involve different pathophysiological mechanisms of regulation at different levels [15,36,37]. Animal studies also revealed that *Hcrt* knockout mice showed decreased energy consumption by reducing spontaneous activities, resulting in increased fat accumulation and obesity [23,38]. Studies of hypothalamic obesity caused by brain tumor revealed that decreased BMR and reduced exercise played an important role [39]. In addition, it has been discovered that sympathetic activity was reduced in adult patients with type 1 narcolepsy, which should be considered a potential impact on metabolism [40]. Our study demonstrated that significantly reduced BMR in the

early stages of the disease substantially contributed to obesity in early type 1 narcolepsy.

This study does have limitations. First, it has been observed that type 1 narcolepsy patients showed rapid increase of weight gain usually within 3 months of onset. However, the patients involved in this study were those who had experienced narcolepsy for 8.67 months (range, 3.5–12 months). Thus, they had already gained weight at the beginning of this study compared to the normal children. Because the control group came from an ordinary primary school in Shanghai, a significant difference existed between the two groups. Second, medications were continued in the patients with narcolepsy. Drugs such as methylphenidate, modafinil, and venlafaxine affect energy metabolism [41–43]. These drugs are normally prone to increase energy metabolism [41–43] and are unlikely to increase the false-positive results. Third, not all of the enrolled patients consistently showed reduced Hcrt-1 in cerebrospinal fluid, and the data were not sufficient to establish a causal relationship between Hcrt-1 deficiency and obesity. Although the 65 patients with narcolepsy with cataplexy met the nocturnal PSG and MSLT diagnostic criteria, only 14 patients agreed to undergo testing for Hcrt-1 in the CSF. The values of all patients were <110 pg/mL. Our Hcrt-1 measurement results are consistent with those in other studies. For example, Han et al. studied a Chinese Han sample with narcolepsy and found that 94.6% of narcoleptic patients with cataplexy showed excessively low Hcrt content in the cerebrospinal fluid [19,44]. Finally, our study did not enroll patients with type 2 narcolepsy, as their body weight was unlikely to significantly change after disease onset [1,28]. In addition, this study did not strictly control dietary intake and exercise activity.

In summary, this longitudinal study revealed the trajectory of weight gain in children with type 1 narcolepsy. BMI growth was significantly increased after onset. With prolonged disease duration, the incidence of obesity was gradually elevated while BMI growth plateaued. The BMR in the patients was reduced by 25% compared with that in the healthy controls, which suggested that BMR decrease was a

key factor underlying rapid weight gain after onset. Furthermore, BMI growth was restored to normal levels 3 to 4 years after the onset of narcolepsy. Simultaneously, BMR was restored to a healthy level. However, very few longitudinal data are available to date. Our discovery of restoration of BMR is consistent with study of Pizza et al. They showed an outline trend on increased overweight/obesity occurrence along the disease course in untreated patients [45]. In view of the irreversible pathologic loss of hypothalamic hypocretin neurons in patients with narcolepsy-cataplexy, further studies are needed to investigate the gradual compensatory mechanisms of BMR during the disease.

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