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Original Article

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

Zongwen Wang [a], Huijuan Wu [a,*], William S. Stone [b], Jianhua Zhuang [a], Linli Qiu [c], Xing Xu [a], Yan Wang [a], Zhengqing Zhao [a], Fang Han [d], Zhongxin Zhao [a,*]

[a] Department of Neurology, Changzheng Hospital, Second Military Medical University, Shanghai, China
[b] Harvard Medical School Department of Psychiatry at Beth Israel Deaconess Medical Center, Boston, MA, USA
[c] School of Sports and Health, East China Normal University, Shanghai, China
[d] Department of Pulmonary Medicine, Beijing University People's Hospital, Beijing, China

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ABSTRACT

Objectives: The aims of this study were 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 six 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 six 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 six, 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 six 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 somnipathy, 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.

* Corresponding authors. Department of Neurology, Changzheng Hospital, Second Military Medical University, 415 Fengyang Road, Shanghai 200003, China. Fax: + 86 21 81885451.
E-mail addresses: huijuan.w@163.com (H. Wu); zhaozx@medmail.com.cn (Z. Zhao).

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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 six 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 six 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 30–40 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 three 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 events/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 non-availability.

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 six 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 seven female, mean age 13.75 ± 2.14 years) at subsequent visit and 16 healthy controls (nine male and seven 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 three 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 I^{125} radioimmunoassay kit (Phoenix Pharmaceuticals, USA) by one of the authors (F.H.) and Dr. Jin Li (Beijing People's Hospital), with standard CSF samples containing known Hcrt-1 levels obtained from Stanford Center for Narcolepsy [16].

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 six-month follow-up were considered baseline data for one-way analysis of variance. All *p* values