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Case Report

Infantile Hypothalamic Hamartoma: A Rare Presentation of Isolated Obesity

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Abstract

Hypothalamic hamartomas (HHs) are rare, benign brain tumors or lesions of the hypothalamus that are predominantly identified in cases of epilepsy and central precocious puberty (CPP), whereas isolated manifestations of infantile obesity are atypical. We herein report an 8-month-old boy with severe obesity (Kaup index 26.4 [>100th percentile]) and uncontrollable hyperphagia. His growth chart demonstrated remarkable weight gain that exceeded the length gain in magnitude. Brain magnetic resonance imaging identified a lesion consistent with HH. There were no episodes or clinical findings of epilepsy, CPP, or Cushing disease. Hypothalamic obesity should be considered in the diagnosis even in infants with excessive weight gain due to overeating.

Key Words: hypothalamic hamartoma, overeating, weight gain, hypothalamic obesity, infant

Abbreviations: ACTH, adrenocorticotropin; CPP, central precocious puberty; GH, growth hormone; HH, hypothalamic hamartomas; HO, hypothalamic obesity; MRI, magnetic resonance imaging; TSH, thyrotropin; GnRH, gonadotropin-releasing hormone; PWS, Prader-Willi syndrome; RR, reference range; WI, weighted image.

Introduction

Hypothalamic hamartomas (HHs) are rare, benign tumors of the central nervous system that develop during the fetal period. The prevalence of HH varies from 1 per 50 000 to 1 per 200 000 individuals, with a slight predominance among boys [1, 2]. Epilepsy, particularly gelastic seizure, is the most common neurological manifestation (90%), followed by cognitive and psychiatric disorders. Central precocious puberty (CPP) accounts for 40% of endocrine manifestations, followed by central hypothyroidism (20%) [3, 4]. CPP caused by HH occurs at a younger age than idiopathic CPP.

Hypothalamic obesity (HO) is also common in patients with HH, with an occurrence rate of approximately 20% to 36% [3, 4], but symptomatic HH associated with obesity is seldom discovered [5-7]. HO is usually diagnosed either at the initial diagnosis of neurological or endocrine disorders or during treatment [8]. To our knowledge, there have been no reported cases of obesity solely attributed to HH in infancy.

We herein report a male infant with HH who exhibited overeating and obesity with no concurrent increase in growth rate. The diagnosis was made based on a lesion in the hypothalamus using brain magnetic resonance imaging (MRI).

Case Presentation

A boy was born at 39 weeks 0 days of gestation without asphyxia as the second child of healthy Japanese parents. His birth weight was 3144 g (57th percentile, +0.17 SD), and his length was 50.0 cm (74th percentile, +0.66 SD). His father was 170 cm tall and weighed 70 kg, his mother was 156 cm tall and weighed 49 kg, and his elder brother (aged 2 years and 10 months) was 98 cm tall (−0.2 SD) and weighed 14.5 kg (Kaup index 15.1 [41.8th percentile]). The patient was completely breast-fed after birth. His development was normal, showing neck stabilization at age 4 months, rolling over at age 6 months, and sitting alone at age 7 months.

He was admitted to the pediatric division of a regional hospital with bronchopneumonia at age 15 days. His Kaup index was 13.4 (74.3th percentile), and feeding was switched from breastfeeding to regular formula during hospitalization. After discharge at age 26 days, he needed to suckle 8 or more times per day, and his feeding volume increased to 60 to 120 mL each session, feeding more than 10 times a day. His weight was 5400 g at age 52 days (weight gain of 68 g/day from the previous 2 weeks). The attending pediatrician advised his mother to reduce the feeding frequency because of his significant weight gain. However, reducing feeding volume proved challenging, as he continued to cry for food and would not sleep without being fed. At age 3 months, he was being fed 1140 mL/day (128 mL/kg/day) of formula, and his Kaup index increased to 19.1 (99.9th percentile) (Fig. 1). At age 5 months, baby food was introduced. Length SD scores decreased from −0.1 SD at age 1 month to −1.5 SD at age 5 months, with insulin-like growth factor-1 levels of 20 ng/mL (reference range [RR],

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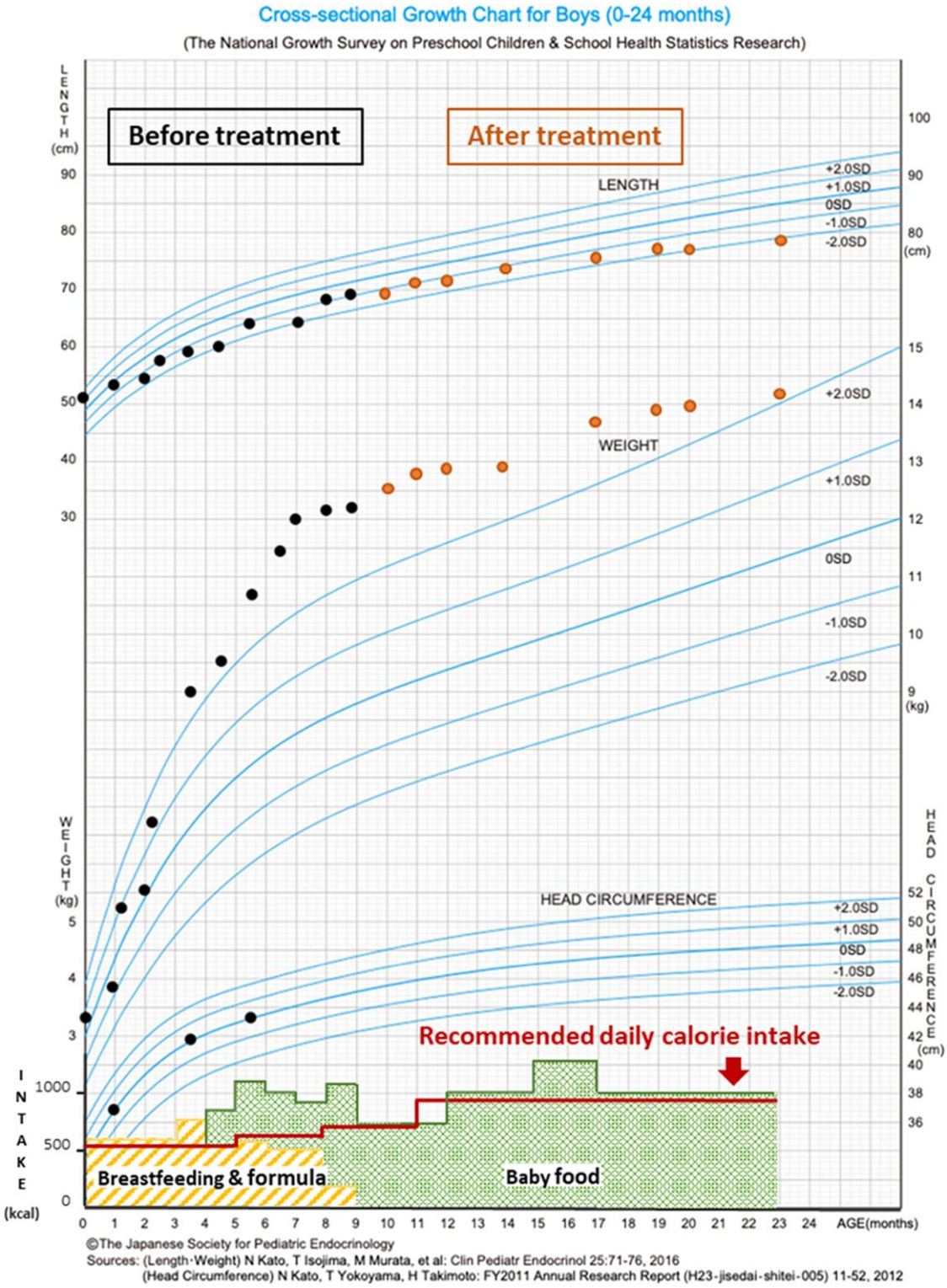

Figure 1. Growth chart and calorie intake of the patient. There was remarkable weight gain and little increase in growth rate from age 1 month. The red line before and after hospitalization indicates the recommended calorie intake by the World Health Organization guideline and the caloric goals of treatment, respectively.

11-149 ng/mL). At age 8 months, his Kaup index reached 26.5 (>100th percentile). Blood tests in the afternoon showed slightly high levels of adrenocorticotropin (ACTH) and cortisol as follows: ACTH 27.9 pmol/L (127 pg/mL) (RR, 1.6-13.9 pmol/L [7.2-63.3 pg/mL]) and cortisol 839 nmol/L (30.4 μg/dL) (RR, 110-550 nmol/L [4.0-20 μg/dL]). Noncontrast brain MRI revealed the presence of a space-occupying lesion in the suprasellar area. The patient was thus referred to our hospital for further evaluation and treatment.

Diagnostic Assessment

On admission, his length was 67.5 cm (−1.2 SD), and his weight was 12.2 kg (Kaup index 26.8 [>100th percentile]). Physical

Figure 2. Photograph of the patient. No central obesity, hirsutism, hyperpigmentation, acne, or striae were observed.

findings were as follows: body temperature, 36.2 °C; blood pressure, 88/62 mm Hg; respiratory rate, 24 beats per minute; pulse, 156 beats per minute; and pulse oxygen saturation value was 100% (room air). Hirsutism, hyperpigmentation, acne, and striae were not observed (Fig. 2). His stretched penile length was 3 cm, and each testicular volume was 1 mL, without pubic hair. His dietary intake consisted of 900 mL of formula daily with 3 servings of daily baby food, totaling more than 1000 calories per day (600 calories are recommended for his age in the World Health Organization guidelines [9]).

After age 2 months, the growth chart indicated that his length fell: Length SD scores were −1.1 SD and −2.4 SD at ages 1 and 7 months, respectively. In contrast, his body weight increased: The Kaup index reached 26.5 (>100th percentile) at age 8 months (see Fig. 1). The representative endocrinological examination data were as follows: Plasma ACTH and serum cortisol levels in the morning were within the normal range; the 24-hour urinary free cortisol values collected on 3 consecutive days were also within the standard normal range. A low-dose dexamethasone suppression test (dexamethasone 3 mg/m2/d for 48 h) showed that endogenous cortisol secretion was adequately suppressed from 155 nmol/L (5.61 μg/dL) to 20.1 nmol/L (0.73 μg/dL) (RR after 48 hours, <49.7 nmol/L [<1.8 μg/dL]). The corticotropin-releasing hormone stimulation test demonstrated normal responses of ACTH and cortisol secretion, with a peak ACTH level of 72.6 pg/mL (16.0 pg/mL) at 15 minutes and a peak cortisol level of 25.2 μg/dL (695 nmol/L) at 30 minutes. Serum tumor markers were all negative (Table 1).

Contrast-enhanced brain MRI revealed a nonenhancing mass lesion measuring 20 mm in the suprasellar region, displaying isointensity on T1-weighted imaging (WI) and slightly higher intensity than the gray matter on T2WI (Fig. 3). Based on these findings, the patient was diagnosed with HH. Electroencephalography [10] revealed no epileptiform abnormalities. Further endocrine assessments revealed an absence of pubertal indices, as evidenced by undetectable basal testosterone level, and an increase in gonadotropins within prepubertal levels by the luteinizing hormone–releasing hormone test; the peak luteinizing hormone level was 3.69 mIU/mL at 30 minutes (RR in prepubertal periods, <5 mIU/mL), which was less than the peak follicle-stimulating hormone level. Stimulation testing with arginine did not trigger growth hormone (GH) secretion with a peak GH level of 1.9 ng/mL (1.9 μg/L) (RR, >6 ng/mL [<6 μg/L]). The thyrotropin-releasing hormone stimulation test showed a normal thyrotropin (TSH) response, with a peak TSH level of 12.7 μIU/mL at 30 minutes (RR, 10-30 μIU/mL).

Table 1. Laboratory data on admission to our hospital

	International system (SI) units (reference range)	Conventional units (reference range)
Glucose	4.2 (2.7-7.8 mmol/L)	75 (50-140 mg/dL)
HbA_{1c}	34 (20-38 mmol/L)	5.3 (4.0%-5.6%)
AFP in blood	3.1 (<20 pg/L)	3.1 (<20 ng/mL)
CA125 in blood	19.2 (<20 U/mL)	19.2 (<20 U/mL)
CA19-9 in blood	<2.06 U/mL (<37 U/mL)	<2.06 (<37 U/mL)
sIL-2R in blood	2124 (157-474 U/mL)	2124 (157-474 U/mL)
HCG-β in blood	ND	ND
HCG-β in CSF	ND	ND
PLAP in CSF	ND	ND
ACTH (at 8AM)	3.2 (1.6-13.9 pmol/L)	14.3 (7.2-63.3 pg/mL)
Cortisol (at 8AM)	154.6 (110-550 nmol/L)	5.6 (4.0-20 μg/dL)
ACTH (at 11PM)	1.8 (1.6-13.9 pmol/L)	8.3 (7.2-63.3 pg/mL)
Cortisol (at 11PM)	375.4 (110-550 nmol/L)	13.6 (4.0-20 μg/dL)
Testosterone	<0.10 (<0.10 nmol/L)	<0.03 (<0.03 ng/mL)
DHEA-S	1.05 (0.30-3.40 μmol/L)	39 (11-125 ng/dL)
TSH	1.84 (0.50-5.00 mIU/L)	1.84 (0.50-5.00 μIU/mL)
Free triiodothyronine	6.14 (4.0-7.8 pmol/L)	4.00 (2.6-5.1 pg/mL)
Free thyroxine	17.1 (12.9-23.2 pmol/L)	1.33 (1.0-1.8 ng/dL)
Urinary free cortisol	(11.8–486 nmol/d)	(4.3-176 μg/d)
(Day 1)	60.7 nmol/d	22.0 μg/d
(Day 2)	73.4 nmol/d	26.6 μg/d
(Day 3)	23.7 nmol/d	8.6 μg/d

Abbreviations: ACTH, adrenocorticotropin; AFP, α-fetoprotein; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19-9; CSF, cerebrospinal fluid; DHEA-S, dehydroepiandrosterone sulfate; HbA_{1c}, glycated hemoglobin A_{1c}; HCG-β, human chorionic gonadotropin-β; ND, not detected; PLAP, placental alkaline phosphatase; sIL-2R, soluble interleukin-2 receptor; TSH, thyrotropin.

Treatment

Based on the clinical characteristics, laboratory data, and imaging information, the infant was diagnosed with HO. We implemented stringent nutritional management based on the standard protocol for Prader-Willi syndrome (PWS) in our outpatient department, with follow-up intervals of every 1 to 2 months.

Outcome and Follow-up

The patient's Kaup index decreased from 27.3 at age 10 months to 22.6 at age 23 months. The growth rate from ages 10 to 23

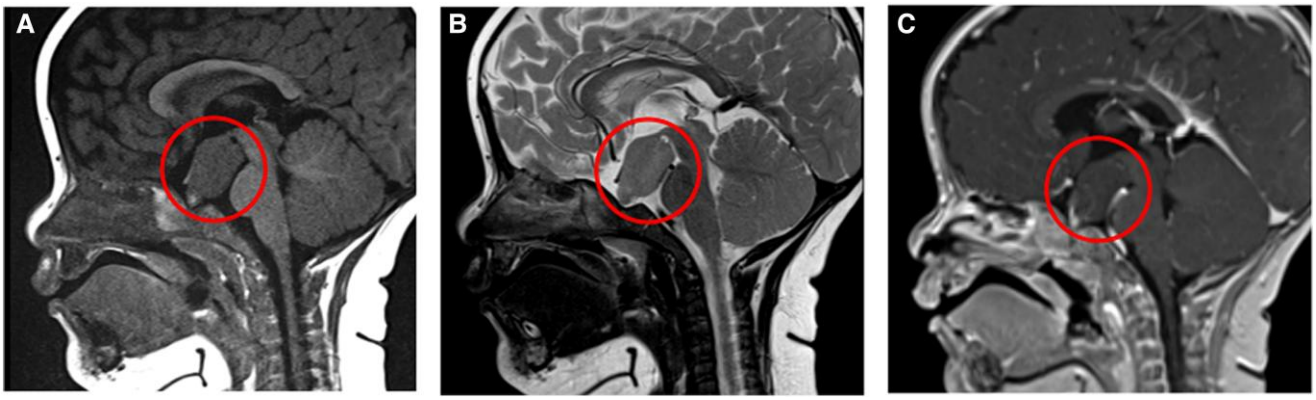

Figure 3. Magnetic resonance imaging of hypothalamic hamartoma (HH) of the patient (A, T1-weighted sagittal image; B, T2-weighted sagittal image; C, T1-weighted sagittal images with contrast agent). A mass lesion approximately 20 mm in size is shown in the suprasellar area. It was isointense compared to the gray matter on T1-weighted imaging (WI) and of slightly higher intensity than the gray matter on T2-WI. No contrast was used.

months was 10.3 cm/year (−1.14 SD), with an insulin-like growth factor-1 level of 16 ng/mL (RR, 14-148 ng/mL). However, food-seeking behavior resembling PWS in childhood was observed on reaching age 1 year; his mother had to secure the pantry due to his frequent attempts to access the food stored therein. The patient did not develop epilepsy or precocious puberty. We plan to conduct reevaluation of the hypothalamic mass lesion using MRI at intervals of approximately 6 to 12 months under careful observation of clinical manifestations.

Discussion

HHs are uncommon tumors of the central nervous system that originate during fetal development. Patients presenting with neurological or endocrinological symptoms typically undergo brain MRI, revealing lesions characterized by contrast enhancement, isointensity relative to gray matter on T1-WI, and hypointensity relative to gray matter on T2-WI [11]. The clinical diagnosis of hamartoma is primarily made without a histopathological examination. Most of these tumors do not exhibit neoplastic proliferation or alterations in size. However, rare cases demonstrate progressive proportional growth of the mass during the early postnatal period to infancy [6].

Although HH does not grow after birth, remarkable obesity frequently appears [12]. Under hypothalamic dysfunction, rapid weight gain due to decreased energy expenditure and increased energy storage in adipose cells can occur from combinations of a reduction in metabolic rate, increased vagal tone, hyperinsulinism with leptin resistance, or sleep disturbance, irrespective of the patient's age [8, 13-16]. Previous studies have reported that girls with CPP accompanied by HH exhibited a higher body mass index than those with idiopathic CPP [17]. In contrast, the body mass index of boys with CPP and HH aligns with that of the general male population [18]. In our case, the diagnosis of HH was based solely on obesity, without the symptoms of CPP or epilepsy, suggesting that obesity by HH may manifest before the onset of neurological or endocrine disorders, even during infancy. In contrast, HH associated with Cushing disease has been rarely reported [19].

Genetic testing may be indicated in patients with early-onset obesity (age <5 years) according to a flowchart in the guideline for pediatric obesity by the Endocrine Society [20]. Although the present case did not have specific clinical findings suggesting genetic obesity syndromes, there remains a possibility of coexisting hereditary obesity-related disorders; therefore, careful monitoring of any characteristic signs of each disorder is important.

The presence of GH deficiency in this case is unclear. Mild GH deficiency might contribute to slow linear growth between ages 1 and 5 months. However, since it is recognized that adiposity negatively influences GH secretion during the stimulation test, severely obese children show diminished GH responses to any stimuli [21]. In addition, GH treatment is contraindicated because of concerns about its potential proliferative effect on tumors, even with GH deficiency. Therefore, careful monitoring of the growth rate would be important for determining GH deficiency.

To our knowledge, there is no specific therapeutic approach for children with HO [14]. Surgical treatment for HH is not recommended because it can cause irreversible damage to the hypothalamus [8]. However, Esquenazi et al [22] reported that a 10-year-old girl with HH and CPP who had refractory overeating and weight gain underwent surgical resection, which resulted in reduced weight gain. This is the only report of successful surgical resection for obesity due to HH.

PWS is a well-known disorder that presents with HO in childhood, and early dietary treatment is effective in preventing overweight [23]. In our case, we provided nutritional guidance on feeding to the parents regularly, at least once a month, from age 2 months, when the patient presented with overfeeding and obesity. Nonetheless, managing the patient's overeating simply by modifying feeding content and amount was extremely difficult. Recent research in the field of pharmacotherapy for HO has made substantial strides, such as the development and application of the glucagon-like peptide-1 analogue liraglutide, melanocortin-4 receptor agonist setmelanotide, and diazoxide choline controlled-release tablets [20, 24]. Further studies will be needed to confirm the safety and effectiveness of these drugs for children with HO.

Learning Points

- Patients with HH can present with isolated remarkable obesity without typical manifestations of epilepsy or precocious puberty.
- The remarkable symptoms of overeating and obesity may suggest the presence of HH, even in infants.
- MRI screening for hypothalamic lesions should be considered in infants who show rapid weight gain without an increase in growth rate.

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Contributors

All authors contributed individually to the authorship of this manuscript; M.T., T.I., M.O., N.H., and N.O. were involved in the diagnosis and management of the patient; M.T., T.I., and K.I. wrote and edited the manuscript; and all authors reviewed and approved the final draft of the manuscript.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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