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Case Report

Adipsic hypernatremia with marked hyperprolactinemia and GH deficiency in a 9-year-old boy

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Highlights

- Hypothalamic dysfunction may develop without intracranial abnormalities in rare cases.
- GH replacement is effective treatment for growth retardation but not for obesity.
- Evaluation of hypothalamic-pituitary function is key to managing adipsic hypernatremia.

Abstract. Adipsic hypernatremia is typically caused by congenital dysplasia of the hypothalamus and pituitary or brain tumors. However, cases of adipsic hypernatremia without underlying organic abnormalities are rare, and some cases have been reported to be complicated by hypothalamic-pituitary dysfunction. The patient in this case was a 9-yr-old boy who was referred to our hospital because of hypernatremia. His growth chart revealed that he had rapidly become obese since infancy, with growth retardation since the age of seven. His hands and feet were very cold, and he had erythema on his abdomen, indicating possible autonomic dysregulation due to hypothalamic dysfunction. Several hormone load tests showed severe GH deficiency (GHD) and marked hyperprolactinemia (peak: 302.8 ng/mL). Magnetic resonance imaging revealed no organic abnormalities in the hypothalamus and pituitary gland. GH replacement therapy was initiated. Although his growth rate improved, obesity persisted. To the best of our knowledge, this is the first report of adipsic hypernatremia without organic intracranial abnormalities that was treated with GH. Moreover, the patient's prolactin levels were higher than those reported in previous studies. In conclusion, adipsic hypernatremia requires the evaluation of pituitary function and appropriate therapeutic interventions.

Key words: adipsic hypernatremia, hypothalamic-pituitary dysfunction, hyperprolactinemia, GH deficiency, obesity

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Introduction

Adipsic hypernatremia is a disorder caused by impaired thirst centers and decreased vasopressin secretion in response to increased plasma osmolality (1). It is generally associated with structural abnormalities of the hypothalamus and the pituitary gland. In contrast, some forms of adipsic hypernatremia do not involve organic intracranial abnormalities and are reported to involve hypothalamic dysfunction, such as thermal dysfunction, and pituitary dysfunction, including GH or thyroid-stimulating hormone (TSH) abnormalities, precocious puberty, or hyperprolactinemia. Furthermore, cases of adipsic hypernatremia with subfornical organ-targeting antibodies have been reported. Here, we report the case of a 9-yr-old boy with adipsic hypernatremia who had remarkable autonomic dysregulation, hyperprolactinemia, and severe GH deficiency (GHD).

Case Report

A 9-yr-old boy with no relevant family history was hospitalized for hypernatremia. He developed erythema reticulatum and cold hands and feet (**Fig. 1A**) at approximately 4 yr of age. Moreover, he was observed to be overweight. Therefore, we carefully monitored his diet and exercise, including forbidding him from receiving second helpings in kindergarten. A medical interview and review of the patient's records during hospitalization revealed no apparent seasonal or diurnal fluctuations in body temperature. Evaluation of the patient's growth history revealed a rapid weight gain between 4 and 9 yr of age. However, no obvious hyperphagia was observed, and the growth rate decreased when he reached 7 yr of age (**Fig. 1B**). The heights of his father and mother were 178 and 155 cm, respectively, and his target height was 173 cm (+0.38 SD). On admission, his height was 123.9 cm (–1.8 SD), and his weight was 40.2 kg (+1.1 SD, body

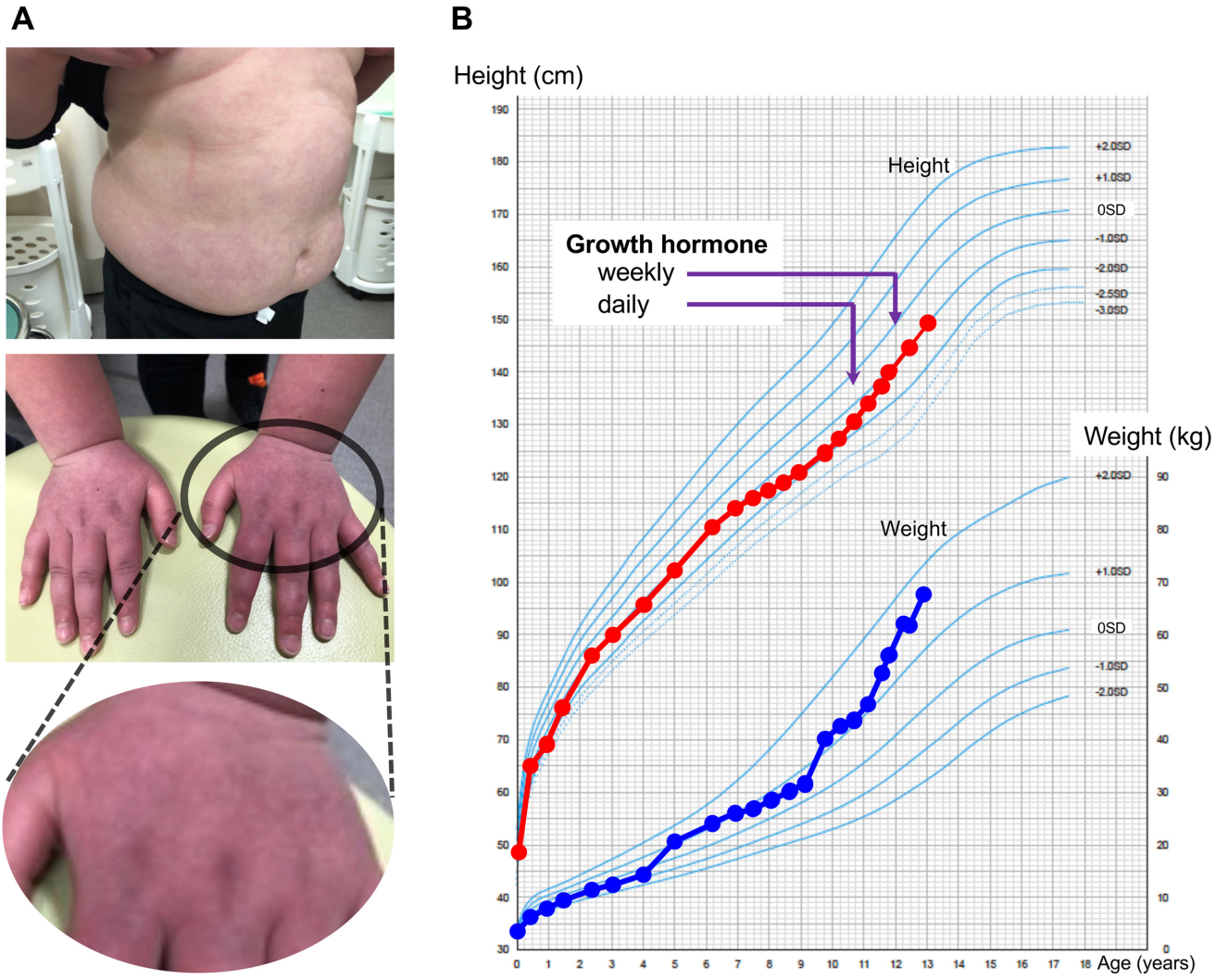

Fig. 1. A: 9-yr-old boy with adipsic hypernatremia with marked hyperprolactinemia and GH deficiency. The patient was severely obese and presented with erythema reticulata. B: The patient's growth history revealed rapid weight gain at four and nine years of age, with a decreased growth rate beginning at seven years of age. After initiating GH replacement therapy at 10 yr and 8 mo of age, the patient's height improved.

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mass index: 26.2). His birth and developmental histories were normal. He was diagnosed with autism at the age of four years and had a full-scale intelligence quotient (FSIQ) score of 70 on the Wechsler Intelligence Scale for Children—Fourth Test. After entering elementary school, he joined a support class for certain subjects. However, subsequent tests showed FSIQ scores of 90 and 100, and he has been attending regular classes without any challenges in his studies or friendships. Blood tests revealed IGF-1 and PRL levels of 72 ng/mL (–2.3 SD) and 320.8 ng/mL, respectively, in addition to hypernatremia (153–159 mEq/L). Macroprolactinemia was ruled out by polyethylene glycol precipitation testing. Mild hepatic dysfunction was also observed (**Table 1**). In the intake interview and history taking, it was noted that he exhibited little thirst despite his hypernatremia. The patient's measured bone age was one year ahead of his actual age. At 9 yr and 10 mo, hormone loading tests (**Table 2**) showed a peak GH level of 0.16 ng/mL at 120 min with insulin loading and 0.17 ng/mL at 60 min with arginine loading, indicating severe GH deficiency. The PRL levels were remarkably elevated at baseline (263.5 ng/mL) and after loading (302.8 ng/mL). No other pituitary hormone levels were abnormal. LH and FSH were at prepubertal levels. Magnetic resonance imaging (MRI) of the head showed no hypothalamic or pituitary lesions. Additionally, the specific antibody responses to the subfornical organ (SFO) and SCAN domain-containing protein 1 were negative. Following GH deficiency (GHD) diagnosis, daily recombinant GH replacement therapy was initiated at 10 yr and 8 mo of age at a dose of 0.015 mg/kg/wk. GH was switched to somapacitan (a long-acting human recombinant GH analog) at 12 yr and 0 mo of age, with a starting dose of 1.5 mg/wk that was increased to 3.0 mg/wk. Two years and 4 mo after GH replacement, his height improved from –1.8 SD to –0.9 SD (**Fig. 1B**). However, obesity and hepatic dysfunction persisted (aspartate aminotransferase, 31 U/L; alanine aminotransferase, 59 U/L). Water intake levels of 1.5–2.0 L/d were required to maintain normal sodium levels (141–148 mmol/L). Subsequent urinalysis indicated adequate urine osmolality; thus, central diabetes insipidus was unlikely, and desmopressin was not administered. Puberty progressed slowly, with a testicular volume of 8 ml at age 13. However, there were no pubic hair or voice changes, and serum testosterone was still undetectable.

Ethical consideration

The patient and his mother provided written informed consent for the publication of this case report and the accompanying images.

Table 1. Results of laboratory and urine analyses

	9-yr-old boy	Reference values
WBC (/μL)	8,000	4,500–13,500
Hb (g/dL)	12.5	10.6–14.4
Plt (/μL)	244,000	150,000–400,000
AST (U/L)	**35**	14–33
ALT (U/L)	**57**	4–23
LDH (U/L)	**353**	120–245
BUN (mg/dL)	18.6	6–20
Cre (mg/dL)	0.62	0.40–0.90
Na (mEq/L)	**153**	138–145
K (mEq/L)	3.8	3.4–4.7
Cl (mEq/L)	**120**	98–106
Serum osmolality (mOsm/L)	**315**	280–290
Urine specific gravity	1.027	1.005–1.030
Urine osmolality (mOsm/L)	972	400–1,500
T-Chol (mg/dL)	180	120–220
LDL (mg/dL)	116	70–140
FBG (mg/dL)	108	70–109
HbA1c (%)	5	4.6–6.2
IGF-1 (ng/mL)	**72**	84–350
freeT4 (ng/dL)	1.13	1.02–1.99
TSH (μIU/mL)	4.53	0.35–4.94
PRL (ng/mL)	**320.8**	4.3–13
LH (mIU/mL)	0.4	–
FSH (mIU/mL)	3.3	–
Testosterone (ng/dL)	< 13	–
PRA (ng/mL·h)	**9.9**	0.3–2.9
Aldosterone (Pg/mL)	152	29.9–159

PRA, plasma renin activity.

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Table 2. Baseline pituitary hormone levels and their responses to intravenous injections of 0.1 U/kg insulin, 2 μg/kg LH-releasing hormone (LH-RH), 5 μg/kg thyrotropin-releasing hormone (TRH), and 5 mL/kg (0.5 g/kg) arginine

	Before	After 15 min	After 30 min	After 60 min	After 90 min	After 120 min
Insulin, LHRH, and TRH loading tests						
BG (mg/dL)	69	58	53	79	82	81
GH (ng/mL)	0.11	0.14	0.13	0.14	0.15	**0.16**
TSH (μIU/mL)	5.1	**16.2**	15.4	11.1	8.1	6.2
PRL (ng/mL)	263.5	**302.8**	283.8	239.2	222.6	243.3
LH (mIU/mL)	0.6	3.7	**5.1**	4.7	4.7	4.4
FSH (mIU/mL)	3.1	5.3	6.9	7.8	8.5	**9.4**
ACTH (pg/mL)	**39.4**	21.9	37.4	38.2	10.3	10.6
Cortisol (μg/dL)	11.4	11	12.2	**18.3**	12.8	10.4
Arginine loading test						
GH (ng/mL)	0.08	None	0.1	**0.17**	0.13	0.1

Discussion

Adipsic hypernatremia, a disease in which patients experience no thirst despite permanently high sodium levels in body fluids, was first recognized in the 1960s (1). Both congenital and acquired adipsic hypernatremia with structural abnormalities of the hypothalamus and pituitary gland have been well documented. Congenital conditions associated with adipsic hypernatremia include midline malformations of the brain (including hypoplasia of the corpus callosum and holoprosencephaly), whereas acquired diseases include Langerhans cell histiocytosis, craniopharyngioma, other brain tumors, and head trauma. Damage to the hypothalamus and the pituitary gland, which contains vasopressin-producing cells, results in decreased secretion of vasopressin into the posterior pituitary gland. This is believed to cause abnormalities in urine volume regulation, leading to chronic hypernatremia. However, reports of adipsic hypernatremia without organic causes have been very rare, with only a few case reports and case series (2–8). To the best of our knowledge, this is the first report of GH therapy in a patient with adipsic hypernatremia without organic intracranial abnormalities. Moreover, the prolactin level in our patient was higher than that reported previously.

The specific pathogenesis of adipsic hypernatremia is unclear, and autoantibodies against Nax and SFO have only been recently demonstrated. Consequently, an autoimmune mechanism has been speculated to be involved in adipsic hypernatremia without structural abnormalities in the hypothalamus and the pituitary gland (9, 10). However, not all cases show positive results for autoantibodies (11), and the present case showed negative results. The prevalence of antibody positivity during the disease-onset period had not been investigated in previous reports, possibly because the SFO antibody had been eliminated during the extended period since the onset of the disease. For example, the patient in this report developed autonomic symptoms and obesity at approximately 4 yr of age; however, antibody analysis was performed at age 9.

Adipsic hypernatremia without structural abnormalities may be associated with manifestations of hypothalamic-pituitary dysfunction such as GHD and hyperprolactinemia (12). However, reports describing GH therapy for GHD are limited. In the present case, after the diagnosis of GHD, daily GH supplementation was commenced at 10 yr of age and switched to weekly somapacitan, a new long-acting human GH analog that became available for adult patients with GHD in Japan in December 2021. The GH dose was gradually increased while monitoring the clinical symptoms and IGF-1 levels, and the effect on the patient's height was evident.

It is necessary to discuss whether secondary sexual characteristics influence the improvement in height. Loading tests showed that the sex hormones were at prepubertal levels at 9 yr and 10 mo, followed by a gradual increase in basal LH and FSH levels; however, testosterone was less sensitive at age 13. Signs of puberty were not examined before GH supplementation; however, at age 13, testicular development was still inadequate, and no changes in pubic hair growth or voice were observed. Generally, a height spurt is not observed in patients with complete GH deficiency, even after the onset of secondary sexual characteristics (13). Considering that puberty progresses slowly, even at age 13, the growth spurt observed in our case may have been due to the contribution of GHs rather than the influence of secondary sexual characteristics. Thus, early GHD diagnosis and treatment are crucial for improving the height prognosis.

Although GH supplementation increased the height of the patient, it did not affect his body mass index or fatty liver. GH supplementation is beneficial for correcting body composition and metabolic disorders and improving the quality of life. It is reportedly effective in patients with idiopathic GHD and those with conditions that cause central obesity, such as Prader-Willi syndrome (14). In the present case, GH supplementation, diet, and exercise

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therapy did not correct the metabolic abnormalities. This may probably be because of individual differences in the effects of GH or underlying diseases such as significant hypothalamic damage.

There is a bilateral relationship between obesity and GHD. Obesity has been reported to cause GHD, causing a hypo-responsiveness of the pituitary gland to a variety of stimuli, including GHRH and other stimuli (15). The present patient also had reduced GH secretion following insulin and arginine stimulation. The patient's GH peak value was 0.17 ng/mL. Given that the standard cutoff value for diagnosing GHD is 6 ng/mL and values below 3 ng/mL are considered severe GHD (16), the value in this case indicates an extremely low response. In several European studies, the GHRH-arginine loading test indicated that the appropriate cut-off points for diagnosing GHD are 11.5 ng/mL, 8.0 ng/mL, and 4.2 ng/mL for BMIs of < 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2, respectively (17). Although this patient was overweight (BMI: 26 kg/m^2), the GH response was too low. Therefore, GHD cannot be diagnosed based on obesity alone. Because GH replacement did not improve the obesity in the present case, it is unlikely that GHD caused the obesity. Therefore, both the obesity and GHD were considered to be primarily due to hypothalamic and pituitary causes, and obesity was not a secondary cause of GHD or vice versa.

With regard to hyperprolactinemia, the PRL level in this case was markedly elevated, although it was mildly elevated (55 ± 32.2 ng/mL) in previous reports (11). However, the significance and pathogenesis of prominent hyperprolactinemia remain unknown. However, serum PRL levels are significantly higher in patients with disease onset at greater than 3 yr of age, suggesting that the timing of the disease onset may play a role in the degree of damage to the SFO of the hypothalamus (11).

The Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation (ROHHAD) syndrome, named by Ize-Ludlow *et al.* in 2007, is a rare childhood syndrome characterized by rapid obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysfunction. Hypothalamic dysfunction has been reported to cause various symptoms, including hypernatremia, hyperprolactinemia, central hypothyroidism, precocious puberty, and adrenocortical dysfunction (18). Although genetic factors have been suggested to cause hypothalamic disorders, an autoimmune mechanism has recently been postulated (19–23). The clinical diagnoses of ROHHAD syndrome and adipsic hypernatremia may overlap, and these two syndromes may share a common pathophysiology (24). In this case, the patient had erythema reticulatum with severe peripheral coldness from 4 yr of age but was treated for chilblains for a long period of time. This may have been an early symptom of autonomic dysfunction. Rapid obesity was observed simultaneously, and a decreased growth rate was observed at approximately 7 yr of age. A detailed evaluation of anterior pituitary function revealed GHD and hyperprolactinemia, which led to the clinical suspicion of ROHHAD syndrome. In patients with ROHHAD syndrome, rapid weight gain persists. In this case, there were two periods of rapid weight gain. This may have been due to the diet and exercise therapy that followed the first weight gain. However, the second weight gain suggests that the effects of obesity associated with the primary disease could not be controlled. The PHOX2B gene, one of the genes responsible for congenital central hypoventilation syndrome, was not analyzed because no symptoms of central hypoventilation, such as apnea, were observed in this case. At the time of writing this report, we had carefully monitored the patient using polysomnography and whole-body MRI for approximately 2 yr and did not observe central hypoventilation or neural crest tumors.

Conclusion

Here, we report the case of a 9-yr-old boy with autonomic dysfunction, obesity, and hypothalamic dysfunction. Pituitary function should be evaluated in patients with adipsic hypernatremia without any organic abnormalities. GH replacement may be considered if GHD is present; however, this treatment does not effectively ameliorate obesity. Early diagnosis and appropriate follow-up based on the characteristic findings may improve the patient's prognosis.

Conflict of interests: The authors indicate no potential conflicts of interest.

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