CASE REPORT

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A Boy with Reset Osmostat Who Developed Chronic Hyponatremia due to Hypothalamic Injury Caused By a Giant Arachnoid Cyst

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What is already known on this topic?

Reset osmostat (RO), a subtype of syndrome of inappropriate antidiuretic hormone (ADH) secretion, is a rare cause of hyponatremia characterized by a decrease in the plasma osmolality threshold for ADH excretion.

What this study adds?

For the first time, we report an 11-year-old boy diagnosed with RO and a giant arachnoid cyst in the prepontine cistern. Sodium correction was considered unnecessary for RO, but chronic hyponatremia must be treated for the risk of decreased bone density and growth obstacles.

Abstract

Reset osmostat (RO) is classified as type C among the four subtypes of the syndrome of inappropriate secretion of antidiuretic hormone based on antidiuretic hormone (ADH) secretion. It is characterized by a lower plasma osmolality threshold for ADH excretion when plasma sodium concentration is reduced. We report the case of a boy with RO and a giant arachnoid cyst (AC). The patient had been suspected of having AC since the fetal period, and a giant AC in the prepontine cistern was confirmed by brain magnetic resonance imaging seven days after birth. During the neonatal period, there were no abnormalities in the general condition or blood tests, and he was discharged from neonatal intensive care at 27 days after birth. He was born with a -2 standard deviation score birth length and mild mental retardation. When he was six years old, he was diagnosed with infectious impetigo and had hyponatremia of 121 mmol/L. Investigations revealed normal adrenal and thyroid functions, plasma hypo-osmolality, high urinary sodium, and high urinary osmolality. The 5% hypertonic saline and water load tests confirmed that ADH was secreted under low sodium and osmolality conditions, and the ability to concentrate urine and excrete a standard water load; therefore, RO was diagnosed. In addition, an anterior pituitary hormone secretion stimulation test was performed, which confirmed growth hormone secretion deficiency and gonadotropin hyperreactivity. Hyponatremia was untreated, but fluid restriction and salt loading were started at 12 years old because of the risk of growth obstacles. The diagnosis of RO is important from the viewpoint of clinical hyponatremia treatment options.

Keywords: Hyponatremia, reset osmostat, syndrome of inappropriate secretion of antidiuretic hormone, arachnoid cyst

Introduction

The human body has a mechanism for maintaining plasma osmotic pressure, volume, and composition homeostasis. Plasma osmotic pressure is primarily regulated by water intake due to thirst and urine volume via antidiuretic hormone (ADH) (1). Therefore, plasma sodium concentrations in healthy people are maintained within a narrow range of 135-145 mmol/L, despite wide variations in water and salt intake (2). In addition, plasma osmolality is closely regulated between 285 and 295 mOsm/kg via a complex interaction between ADH secretion and

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action and the sensation of thirst, which promotes water intake (2). The hypothalamus, which contributes to the osmotic control of thirst and salt appetite, partly mediates behavioral responses (3). The hypothalamus also regulates neuroendocrine responses by regulating the rate of renal sodium and water excretion through changes in the release of neurohypophysial natriuretic hormone and ADH (4).

Hyponatremia, a serum sodium level < 135 mmol/L, is the most common electrolyte disorder encountered in clinical practice (5). Hyponatremia has several etiologies and can be classified into hypotonic hyponatremia (further classified as hypovolemic, euvolemic, or hypervolemic), pseudohyponatremia, and non-hypotonic hyponatremia. Euvolemic hyponatremia is caused by an increase in the relative absolute volume of body water, and the syndrome of inappropriate antidiuresis (SIADH) is the most common cause of euvolemic hyponatremia in hospitalized patients (5). SIADH has a vast spectrum of etiologies and differential diagnoses and has classically been divided into four types (A, B, C, and D) (6). Type A is characterized by high erratic fluctuations in ADH that are not physiologically affected by plasma osmolality. Type B involves elevated basal secretion of vasopressin despite normal regulation by osmolality. Type C is a rare condition called reset osmostat (RO), which is characterized by a decrease in the plasma osmolality threshold for ADH excretion. Type D is characterized by normal osmoregulation of ADH; these cases relate to V2R receptor mutations that lead to constitutive activation of the receptor in the absence of ADH (7).

Type C, or RO, is infrequently encountered and poorly recognized. Unlike traditional SIADH, RO lowers the osmotic threshold for ADH release while maintaining the tubular volume of dilution and urine concentration (6). Herein, we report the case of an 11-year-old boy who had a giant arachnoid cyst (AC) that pressed on the hypothalamus in the prepontine cistern, and he was diagnosed with RO due to chronic hyponatremia.

Case Report

This was the case of an 11-year-old boy. During the 27th week of pregnancy, ACs were identified. The patient was born via cesarean section at 38 weeks and 3 days gestation, with a birth length of 49 cm and weight of 3.477 g. Apgar scores were 9 and 10 at 1 min and 5 min, respectively. At seven days after birth, a giant AC was confirmed in the prepontine cistern using brain magnetic resonance imaging (MRI). Respiratory and circulatory functions were maintained, and oral feeding was adequate. Blood tests revealed no abnormalities in electrolytes (serum sodium level was 138-142 mmol/L), blood glucose level, or blood count, and the patient was discharged on the 27th day after birth.

The AC tended to expand temporarily on MRI during infancy; however, there was no evidence of increased intracranial pressure, and the size of the AC did not change after about a year, and thus the progression was observed without surgery. He had a mild developmental delay in early childhood and had an intelligence quotient of 87 at five years of age. In addition, he grew with a short stature of about -2 standard deviations (SD). When he visited an outpatient clinic for infectious impetigo at 6 years and 1 month, a serum sodium level of 121 mmol/L was discovered, indicating hyponatremia. Initially, SIADH was suspected, and the patient was admitted to hospital with water restriction (15 mL/kg/day), 3% hypertonic saline load (7.4 mEq/kg/day), and administration of diuretics (1 mg/kg of intravenous furosemide). The serum sodium level temporarily increased to 134 mmol/L; however, it decreased to 125 mmol/L after treatment. His general condition was stable, and he was subsequently discharged from the hospital. One month later, he was re-examined for hyponatremia. During a physical examination at 6 years and 2 months of age, his height was 104.6 cm (-2.1 SD), weight was 16.6 kg, and body mass index was 15.2. He had clear consciousness and no skin swelling or edema. The blood pressure was 111/64 mmHg, pulse rate was 95 beats/min, temperature was 36.7 °C, and SpO_2 level was 98% (room air). The external genital Tanner classification was 1, and the testis volume was 1 cm^3 bilaterally. Red blood cell count was 3.94×10^4/μL, hemoglobin was 10.9 g/dL, hematocrit was 30.5%, white blood cell count was 6,500/mm^3, and platelets were 484,000/mm^3. The venous blood gas analysis was normal. Serum sodium was 127 mmol/L, serum potassium was 4.5 mmol/L, serum chlorine was 94 mmol/L, blood urea nitrogen was 14 mg/dL, uric acid was 2.1 mg/dL, creatinine was 0.19 mg/dL, and fasting blood glucose was 90 mg/dL. There were no abnormalities in hormones, including thyroid and adrenal hormones, with adrenocorticotropic hormone of 10.8 pg/mL, cortisol of 18 μg/dL, free triiodothyronine of 2.76 pg/mL, free thyroxine of 1.05 ng/dL and thyroid-stimulating hormone, 2.44 μIU/mL. However, the insulin-like growth factor was 32 ng/mL, which was low for his age. Testosterone was < 0.02 ng/mL, follicle-stimulating hormone basal value was 0.95 μIU/mL, and luteinizing hormone (LH) basal value was 0.60 IU/mL, which were pre-pubertal values. Urinalysis revealed a specific gravity of 1.028, pH of 7.0, glucosuria (-), and proteinuria (±). Urine biochemistry had a urinary sodium and creatine level of 170 mmol/L and 75 mg/dL, respectively.

When the brain MRI was re-examined and compared with the previous year, the size of the AC in the prepontine cistern, the degree of enlargement of the bilateral ventricles, and the findings of hypothalamus-pituitary stalk exclusion to the cranial side were unchanged (Figure 1).

When he complained of thirst, a biochemical blood test revealed that his serum sodium level was 125 mmol/L, and plasma osmolality was 266 mOsm/kg. Subsequently, a 5% hypertonic saline load test (infused over 120 min at a dose rate of 0.05 mL/kg/min) was performed. The values before and 60, 120, and 180 min after hypertonic saline loading were: serum sodium level, 127-132-134-135 mmol/L; plasma osmolality, 262-267-271-275 mOsm/kg; urine osmolality, 853-618-566-618 mOsm/kg; and ADH level, 2.4-1.8-2.1-14.1 pg/mL, respectively. This confirmed that low serum sodium and plasma osmolality increased ADH secretion.

Based on the results, we suspected type C SIADH and conducted a water load test (Figure 2). After drinking 350 mL (≈20 mL/kg) of water, 294 mL (84% of water intake) of urine was observed after 4 h, and diluted urine with a urine osmotic pressure of 61 mOsm/kg was confirmed. Furthermore, the fraction of urate excretion (FEUa) measured during the course of the test was 7.9%. From these results, the cause of chronic hyponatremia was diagnosed as RO.

In addition, the patient had a short stature and underwent an anterior pituitary hormone secretion stimulation test (Figure 3). He had no abnormalities in thyrotropin-releasing hormone or corticotropin-releasing hormone secretion. However, he was diagnosed with moderate growth hormone (GH) deficiency (GHD) because he had a peak GH value of 3.69 ng/mL on a clonidine load test. In addition, even before puberty, a LH-releasing hormone loading test confirmed a gonadotropin overreaction with LH as the predominant hormone.

After the examination, he was discharged from the hospital and followed-up at the outpatient department. Subsequently, the serum sodium level has remained around 120 mmol/L. There were occasional complaints of headache and vomiting but brain MRI revealed no evidence of the AC expanding. He has been on follow-up and has been encouraged to maintain mild fluid restriction and salt intake for his hyponatremia. GHD was initially followed-up with no hope of effective treatment, but his parents persisted. Thus, we commenced GH injections at 11 years and four months. At this age, the external genital Tanner stage was 1, and the testis volume was 1 cm^3 bilaterally, and physical findings revealed no signs of precocious puberty.

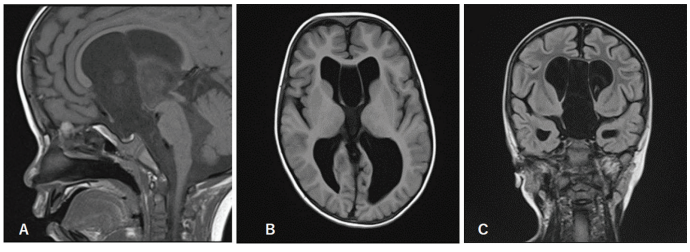

Figure 1. Brain magnetic resonance imaging. A) Sagittal section, T1W1; B) Coronal section, fluid attenuated ınversion recovery; C) Cross section, T1W1. The hypothalamus and pituitary stalk are anteriorly excluded by a giant arachnoid cyst in the prepontine cistern

Discussion

Hyponatremia (serum sodium level of less than 135 mmol/L) is caused by three mechanisms: inability to excrete water loads, excessive sodium loss, or inadequate sodium intake (8). As an algorithm for diagnosing hyponatremia, one should confirm whether it is isotonic, hypotonic, or

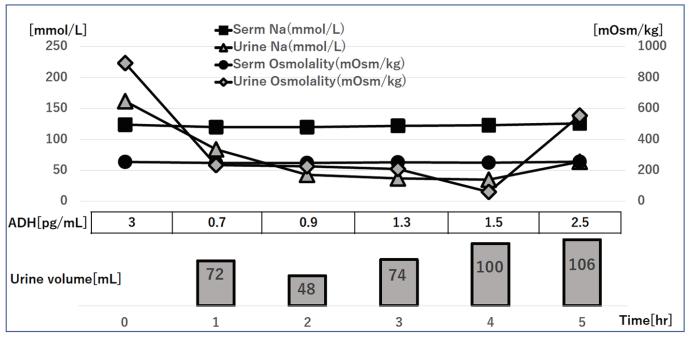

Figure 2. Effect of 350 mL (≈20 mL/kg) water load test. There was 294 mL (≈84%) of urine excretion in 4 h, and the urine osmolality was below 100 mOsm/kg

ADH: antidiuretic hormone

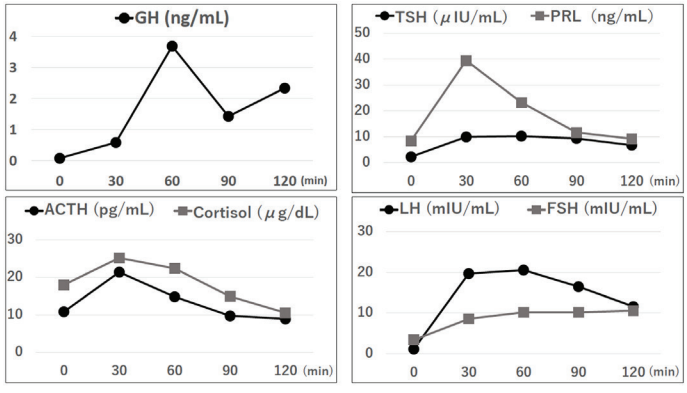

Figure 3. Clonidine/thyrotropin-releasing hormone/corticotropin-releasing hormone/luteinizing hormone-releasing hormone stimulation test. The results demonstrated growth hormone deficiency and gonadotropin overreaction

GH: growth hormone, TSH: thyroid-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, PRL: prolactin

hypertonic before proceeding with the differential diagnosis (8). Hypotonic hyponatremia is further classified as hypovolemia, euvolemia, or hypervolemia and should be differentiated according to the urinary sodium level of 20 mmol/L more or less (9). Hyponatremia is typically treated by suppressing ADH secretion, resulting in the excretion of maximally diluted urine (≤100 mOsm/kg). Most patients with hyponatremia and hypo-osmolarity are unable to retain water due to continuous ADH secretion, even though their urinary osmolality is above 100 mOsm/kg and density is above 1.003 (6). This euvolemic hyponatremia is the cause of 60% of all types of chronic hyponatremia, with SIADH being the most common cause, and other causes include hypothyroidism, glucocorticoid deficiency, and inadequate fluid therapy (6). The diagnostic criteria for SIADH described by Bartter and Schwartz (7) in 1967 are hyponatremia with plasma hypo-osmolarity, high urinary osmolality relative to plasma osmolality, increased urinary sodium excretion, absence of edema or volume depletion, and normal renal and adrenal functions (9). All of the criteria were met in the presented case.

The diagnostic criteria for RO include normovolemic hypotonic hyponatremia; normal renal, adrenal, and thyroid function; ability to concentrate urine; ability to excrete a standard water load, with excretion of more than 80% within four hours; maintenance of urine osmolality at or below 100 mOsm/kg during sustained water diuresis; and maintenance of normal sodium balance salt loading (10). The presented patient met these diagnostic criteria, and the water load test was crucial in diagnosing RO (11), with 84% of the loaded water content urinated within four hours. In addition, RO should exhibit a normal FEUa (4-11%) (12), which was noted in our patient (7.9%). First, a common cause of RO could be damage to the posterior pituitary (13). Changes in plasma osmotic pressure are caused by changes in the balance between the ingress and egress of electrolytes and water into the living body and are detected by osmotic receptors in the anterior hypothalamus (14). The osmotic receptors are present in the late paraventricular and subfornical organs of the anterior paraventricular nucleus of the third ventricle, and an increase in plasma osmotic pressure is detected at these sites, and the hypothalamus paraventricular nucleus and supraoptic nucleus. The signal is transmitted to the ADH neurons, and the posterior hypothalamus promotes ADH secretion (15).

Changes in osmolality are susceptible to changes in ADH secretion, and even a 1% increase in plasma osmolality increases ADH secretion (16). Moreover, there is an osmotic pressure threshold for ADH secretion, and ADH secretion is normally inhibited when the plasma osmotic pressure is about 280 mOsm/kg H_2O or less (16). When plasma osmolality exceeds this threshold, ADH secretion increases linearly (16). In addition, when the plasma osmotic pressure is approximately 290 mOsm/kg H_2O or higher, the thirst center is stimulated to induce drinking behavior, which contributes to the maintenance of body fluid volume as well as an increase in ADH secretion (16). Head trauma or intracranial lesions cause an abnormal resetting of these strict mechanisms of hypothalamic osmoreceptors, resulting in an inappropriate antidiuretic response to perceiving lower serum sodium levels. In case presented here, results consistent with RO findings in the hypertonic saline loading test were noted. The temporary decrease in ADH level, despite a mild increase in plasma osmolality, at 60 minutes after loading may have been due to the addition of water loading to the preload dehydration situation, in addition to the sodium loading.

Case reports of RO are rare, and pediatric reports are even rarer. The majority are also associated with median defects, such as cleft lip and palate, corpus callosum agenesis, pituitary disorder, and hypothalamic cysts (6,17,18,19). In the presented patient, the giant AC in the prepontine cistern displaced the anterior ventricular wall of the third ventricle, including the paraventricular nucleus of the hypothalamus, which is involved in ADH secretion.

Our case suggests that the cause of RO may be an abnormal reset of the hypothalamic osmoreceptor. The second possibility is sick cell syndrome. “Sick cells” have less effective osmotic pressure and thus their volume decreases, triggering vasopressin release. In severe hyponatremia, the release of ADH to retain water inside the cells is high; consequently, these cells begin to swell, exceeding their original size and inhibit lowering of serum sodium levels (20).

Previously, it was thought that correction of hyponatremia was unnecessary in RO because increased plasma sodium level and osmolality promote ADH secretion (21). However, recent evidence in adults suggests that chronic hyponatremia is associated with attention deficits (22), cognitive impairments (23), bone fractures, and osteoporosis (24). Hyponatremic rats showed decreased bone mineral density, in both trabecular and cortical bones, and significantly increased osteoclast activity (25). Although our patient presented with short stature, the GHD was moderate, as revealed by the GH secretion stimulation test results. Furthermore, no significant decrease was noted in the growth rate without GH treatment until the age of 11 years and 4 months. After initiation of GH treatment, his growth rate was increased slightly. In addition, bone mineral density performed by dual energy X-ray absorptiometry in the lumbar spine (L1-L4) was 0.470 g/cm^2 at 12 years

of age, with an age-matched Z-score of -5.1. Thus, we also considered the possibility that the effect of chronic hyponatremia, in addition to GHD, on bone resulted in short stature. In a report of an 8-year-old girl with a hypothalamic glioma complicated by RO who had difficulty with fluid restriction, oral administration of tolvaptan, an arginine vasopressin V2 receptor antagonist, showed improvement in hyponatremia and relief of fluid restriction (19). At present, data on the use of tolvaptan in children are limited, and caution must be exercised during long-term use, especially with regard to the side effect of liver dysfunction due to hepatotoxicity. However, there is also a report that suggests that oral tolvaptan was safely administered to three pediatric patients with chronic hyponatremia due to SIADH (26).

To the best of our knowledge, the present study is the only case report of a child with severe hyponatremia caused by RO due to an AC. This patient was initially thought to have no need for treatment to correct hyponatremia due to RO. However, to avoid adverse events caused by chronic hyponatremia, which have become evident in recent years, it is necessary to restrict salt and excessive fluid intake and to continue careful monitoring of the patient's progress, while considering tolvaptan administration.

Conclusion

In asymptomatic patients with severe hyponatremia, RO should be considered. RO is uncommon and very rare in children. In this present case, RO may have been induced by physical pressure on the hypothalamus or by a disability. Further case series and studies are warranted to define the need for treatment of chronic hyponatremia caused by RO in children.

Ethics

Informed Consent: Informed consent was obtained from the parent of the patient for publication of this case.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Junko Naganuma, Satomi Koyama, Yoshiyuki Watabe, Concept: Junko Naganuma, Design: Junko Naganuma, Data Collection or Processing: Junko Naganuma, Satomi Koyama, Analysis or Interpretation: Junko Naganuma, Satomi Koyama, Yoshiyuki Watabe, Shigemi Yoshihara, Literature Search: Junko Naganuma, Writing: Junko Naganuma.

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