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Isolated Adrenocorticotropic Hormone Deficiency Presenting with Severe Hyponatremia and Rhabdomyolysis: A Case Report and Literature Review

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 67-year-old
Final Diagnosis: Isolated adrenocorticotropic hormone deficiency
Symptoms: Anorexia • fatigue • vomiting • muscle weakness
Medication: —
Clinical Procedure: Dynamic endocrine testing
Specialty: Endocrinology and metabolic

Objective: Rare co-existance of disease or pathology

Background: Isolated adrenocorticotropic hormone deficiency (IAD) is a rare disorder characterized by central adrenal insufficiency (AI) but normal secretion of pituitary hormones other than adrenocorticotropic hormone. IAD usually presents with unspecific symptoms of AI, such as anorexia and fatigue, but some patients present with a variety of atypical manifestations. Rhabdomyolysis is a potentially life-threatening clinical syndrome caused by skeletal muscle injury with the release of muscle cell contents into the circulation. A wide variety of disorders can cause rhabdomyolysis. Herein, we report an unusual case of IAD presenting with hyponatremia and rhabdomyolysis.

Case Report: A 67-year-old Japanese woman with a 2-month history of anorexia and fatigue was diagnosed with severe hyponatremia (serum sodium, 118 mEq/L) and rhabdomyolysis (serum creatine phosphokinase, 6968 IU/L), after 2 days of vomiting and muscle weakness. Physical and laboratory findings did not show dehydration or peripheral edema. Her rhabdomyolysis resolved with normalization of serum sodium levels during administration of sodium chloride. However, her anorexia and fatigue remained unresolved. After reducing the amount of sodium chloride administered, the patient still had hyponatremia. Detailed endocrinological examinations indicated IAD; her hyponatremia was associated with inappropriately high plasma arginine vasopressin levels. The patient received corticosteroid replacement therapy, which resolved her anorexia, fatigue, excessive arginine vasopressin, and hyponatremia.

Conclusions: This case highlights the importance of considering the possibility of central AI in patients with hyponatremia and excessive arginine vasopressin levels. In addition, rhabdomyolysis associated with hyponatremia can be an important manifestation of IAD.

MeSH Keywords: Adrenal Insufficiency • Empty Sella Syndrome • Arginine Vasopressin • Hydrocortisone • Hyponatremia • Rhabdomyolysis

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Background

Adrenal insufficiency (AI) is an endocrine disorder characterized by glucocorticoid deficiency (hypocortisolemia) [1]. Clinical manifestations of AI include anorexia, fatigue, lethargy, fasting hypoglycemia, anemia, and electrolyte imbalance. AI can be caused by either destruction of the bilateral adrenal cortex (primary AI) or a deficiency of adrenocorticotropic hormone (ACTH) attributable to disturbed hypothalamic-pituitary axis (central AI). Primary AI is characterized by a deficiency of all adrenocortical hormones, including mineralocorticoids, and often presents with hyperkalemia and hyponatremia, principally attributable to renal sodium loss [2]. Central AI is not associated with mineralocorticoid deficiency, but patients may exhibit impaired water excretion and dilutional hyponatremia as a result of hypocortisolemia-related excessive secretion of the antidiuretic hormone, arginine vasopressin (AVP) [3,4].

Isolated adrenocorticotropic hormone deficiency (IAD) is a rare pituitary disorder characterized by central AI but normal secretion of pituitary hormones other than ACTH [5]. Because patients with IAD usually present with diverse and unspecific AI symptoms, early diagnosis remains a challenge in many cases. IAD may also present with a variety of atypical manifestations, such as flexion contractures of the legs [6] or widespread musculoskeletal pain [7].

Rhabdomyolysis (RM) is a potentially life-threatening syndrome resulting from skeletal muscle injury with the leakage of muscle cell contents into the circulation [8–10]. Patients may experience muscle weakness, muscle aches, fatigue, and vomiting, with or without acute kidney injury. RM is usually diagnosed based on biochemical test results showing high serum creatine phosphokinase (CPK) levels. RM can be caused by direct muscle injury as well as toxins, alcohol abuse, medications, and a wide variety of diseases. Cases of hyponatremia and RM in patients with primary AI [11] or central AI [12–17] have been reported.

Herein, we report an unusual case of IAD presenting with severe hyponatremia and RM. In addition, previously reported cases of hyponatremia and RM in patients with central AI are reviewed.

Case Report

A 67-year-old Japanese woman was admitted to a local hospital in August 2018 because of severe hyponatremia and RM. The patient's past medical and family histories were unremarkable. The patient had never smoked cigarettes or consumed alcohol. She never had a brain tumor, head surgery, or radiation therapy, and never took medications that can cause RM or AI, such as antihyperlipidemic agents, psychiatric agents, or corticosteroids. The patient was healthy until June 2018, when she developed anorexia and fatigue without headache or head trauma. Two months later, she was taken by ambulance to a local hospital in August 2018 after 2 days of vomiting and muscle weakness without pain, which occurred without excessive muscle exertion or trauma. The patient had clear consciousness, and her body temperature, blood pressure, and pulse rate were 36.3°C, 150/94 mmHg, and 74 beats per minute, respectively. She did not exhibit symptoms indicative of viral or bacterial infection, such as headache, throat pain, cough, abdominal pain, diarrhea, joint pain, or skin rash. The patient had no physical signs of dehydration, such as dry oral cavity or poor skin turgor. No peripheral edema was found. Blood chemistry findings (Table 1) showed high levels of CPK, aspartate aminotransferase, lactate dehydrogenase, C-reactive protein, low levels of sodium, plasma osmolality (Posm), and fasting plasma glucose, and normal levels of free thyroxine (FT_4), free triiodothyronine (FT_3), and thyroid-stimulating hormone (TSH). A troponin test was negative, and electrocardiography revealed no ST segment abnormalities. Urine dipstick was positive for blood, but no red blood cells were found on microscopy, suggesting myoglobinuria. The patient was diagnosed with hyponatremia and RM and was admitted to the local hospital. After infusion therapy with normal saline (500 mL), her serum sodium levels did not increase. Because the urinary osmolality was relatively high (Table 1), her hyponatremia was considered possibly associated with excessive secretion of antidiuretic hormone [2]. The patient received intravenous 3% hypertonic saline solution followed by oral sodium chloride administration. Her vomiting and muscle weakness resolved 3 days after admission. On day 5 after admission, serum sodium (136 mEq/L) and CPK (131 IU/L) levels normalized, indicating resolution of RM. However, the patient continued to experience anorexia and fatigue, and after reducing the amount of oral sodium chloride administered, hyponatremia persisted. In addition, a low basal serum cortisol level (Table 1) was revealed. The basal serum cortisol remeasured on day 21 after admission was lower (0.3 µg/dL). Twenty-seven days after admission, she was transferred to our hospital in September 2018 for further endocrinological examination and management.

On physical examination at the time of transfer, the patient's height, weight, temperature, blood pressure, and pulse rate were 146 cm, 34.6 kg (body mass index, 16.2 kg/m^2), 36.5°C, 99/58 mmHg, and 59 beats per minute, respectively. No dry oral cavity, poor skin turgor, thyromegaly, chest rales, heart murmur, abdominal tenderness, or peripheral edema were observed. Although the patient had a mild appetite loss, every meal was completely consumed, which provided 10 g/day of dietary salt. In addition, she was administered oral sodium chloride (6 g/day).

Blood chemistry (Table 1) showed low levels of ACTH, cortisol, and dehydroepiandrosterone sulfate, but normal levels of

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Table 1. Laboratory findings.

	On admission to a local hospital (August 2018)		On transfer to our hospital (September 2018)	
Hematology				
Red blood cells (×10⁴/μL)	424	(370–470)	308	(386–492)
Hemoglobin (g/dL)	11.8	(11.5–14.5)	8.6	(11.6–14.8)
Hematocrit (%)	32.8	(34.0–42.0)	25.9	(35.1–44.4)
White blood cells (/μL)	4400	(4000–9000)	2700	(3300–8600)
Platelets (×10⁴/μL)	19.4	(15.8–34.8)	21.4	(15.8–34.8)
Blood chemistry				
Total protein (g/dL)	6.9	(6.7–8.3)	5.8	(6.6–8.1)
Albumin (g/dL)	4.4	(3.8–5.3)	3.6	(4.1–5.1)
Aspartate aminotransferase (IU/L)	110	(8–38)	140	(13–30)
Lactate dehydrogenase (IU/L)	413	(109–218)	203	(124–222)
Creatine phosphokinase (IU/L)	6968	(13–142)	52	(41–153)
Urea nitrogen (mg/dL)	7.1	(8.0–20.0)	7.7	(8.0–18.4)
Creatinine (mg/dL)	0.43	(0.37–1.00)	0.53	(0.46–0.79)
Sodium (mEq/L)	118	(135–147)	133	(135–145)
Potassium (mEq/L)	4.1	(3.5–4.8)	4.0	(3.5–4.8)
Chloride (mEq/L)	87	(98–108)	100	(98–108)
C-reactive protein (mg/dL)	2.63	(0–0.30)	0.82	(0–0.14)
Triglycerides (mg/dL)	N.M.		172	(50–149)
Fasting plasma glucose (mg/dL)	64	(70–109)	79	(70–109)
Plasma osmolality (mOsm/kg)	243	(270–290)	269	(275–290)
Endocrinology				
Arginine vasopressin (pg/mL)	N.M.		0.9	*
Thyroid-stimulating hormone (μIU/mL)	4.35	(0.35–4.94)	11.08	(0.50–5.00)
Free thyroxine (ng/dL)	1.19	(0.70–1.48)	0.98	(0.90–1.70)
Free triiodothyronine (pg/mL)	2.33	(1.71–3.71)	2.61	(2.30–4.00)
Adrenocorticotropic hormone (pg/mL)	3.1	(7.2–63.3)	3.6	(7.2–63.3)
Cortisol (μg/dL)	0.7	(4.5–21.1)	< 0.2	(4.5–21.1)
Plasma renin activity (ng/mL/h)	1.1	(0.2–2.3)	0.5	(0.2–2.3)
Aldosterone (ng/dL)	10.0	(3.0–15.9)	3.8	(3.0–15.9)
Dehydroepiandrosterone sulfate (ng/mL)	N.M.		< 20	(120–1330)
Urine chemistry				
Urinary osmolality (mOsm/kg)	633	(50–1300)	550	(50–1300)
Urinalysis				
Occult blood	Positive		Negative	
Protein	Negative		Negative	
Leukocytes	Negative		Negative	

Blood and urine samples were taken with the patient in a supine position at 8 AM, the time of admission to a local hospital (August 2018), and at 9 AM, the time of transfer to our hospital (September 2018). The reference range for each parameter is shown in parentheses. * The reference range for plasma arginine vasopressin level, which depends on the plasma osmolality levels [2], is undetectable for low plasma osmolality levels. N.M. – not measured.

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Table 2. Endocrinological investigation (September 2018).

A. Rapid cosyntropin stimulation test.

	Time (min)		
	0	30	60
Cortisol (μg/dL)	< 0.2	2.5	3.2
Aldosterone (ng/dL)	7.3	11.7	16.0

Synthetic adrenocorticotropic hormone 1–24 (cosyntropin hydroxide 0.25 mg) was intravenously administered in the morning (9 AM).

B. CRH/GRF/TRH/LHRH stimulation test.

	Time (min)					
	0	15	30	60	90	120
Adrenocorticotropic hormone (pg/mL)	2.8	2.2	2.7	3.0	2.8	3.0
Cortisol (μg/dL)	0.6	0.7	0.7	1.1	1.0	0.8
Growth hormone (ng/mL)	0.8	5.7	10.0	17.0	17.8	11.6
Thyroid-stimulating hormone (μIU/mL)	8.3	54.0	67.3	55.4	43.1	33.9
Prolactin (ng/mL)	28.7	104.1	128.5	115.2	82.5	70.4
Luteinizing hormone (mIU/mL)	8.3	11.4	13.6	18.8	20.9	20.5
Follicle-stimulating hormone (mIU/mL)	22.0	24.2	25.1	26.6	28.6	28.1

The following synthetic hypothalamic hormones were intravenously administered in the morning (9 AM): human corticotropin-releasing hormone (CRH; 100 μg), growth hormone-releasing factor (GRF; 100 μg), thyrotropin-releasing hormone (TRH; 500 μg), and luteinizing hormone-releasing hormone (LHRH; 100 μg).

C. GHRP-2 stimulation test.

	Time (min)				
	0	15	30	45	60
Adrenocorticotropic hormone (pg/mL)	2.1	4.2	3.3	4.0	3.8
Cortisol (μg/dL)	0.3	0.3	0.3	0.4	0.3
Growth hormone (ng/mL)	0.7	8.6	9.8	7.0	4.7

Growth hormone-releasing peptide-2 (GHRP-2; 100 μg) was intravenously administered in the morning (9 AM).

plasma renin activity and aldosterone. Her plasma AVP level was inappropriately high given her low serum sodium and Posm [2]. The serum FT_4 and FT_3 levels were normal; however, her TSH level was high.

A rapid cosyntropin stimulation test showed an insufficient cortisol response, whereas the aldosterone secretion was sufficient (Table 2A), suggesting central AI. Dynamic tests on secretion of anterior pituitary hormones showed normal secretion of growth hormone, TSH, and prolactin, as well as age-appropriate secretion of luteinizing hormone and follicle-stimulating hormone; the ACTH secretion was insufficient after the corticotropin-releasing hormone load (Table 2B). A growth hormone-releasing peptide-2 loading test also showed an insufficient ACTH release, whereas growth hormone release was normal (Table 2C). These findings indicated IAD.

Brain magnetic resonance imaging showed no abnormalities in the cerebral cortex, cerebellum, or brainstem, but revealed an empty sella turcica (Figure 1). An ultrasound of the thyroid gland revealed no abnormalities. Computed tomography of the abdomen showed no abnormalities in the liver, spleen, pancreas, kidneys, or adrenal glands.

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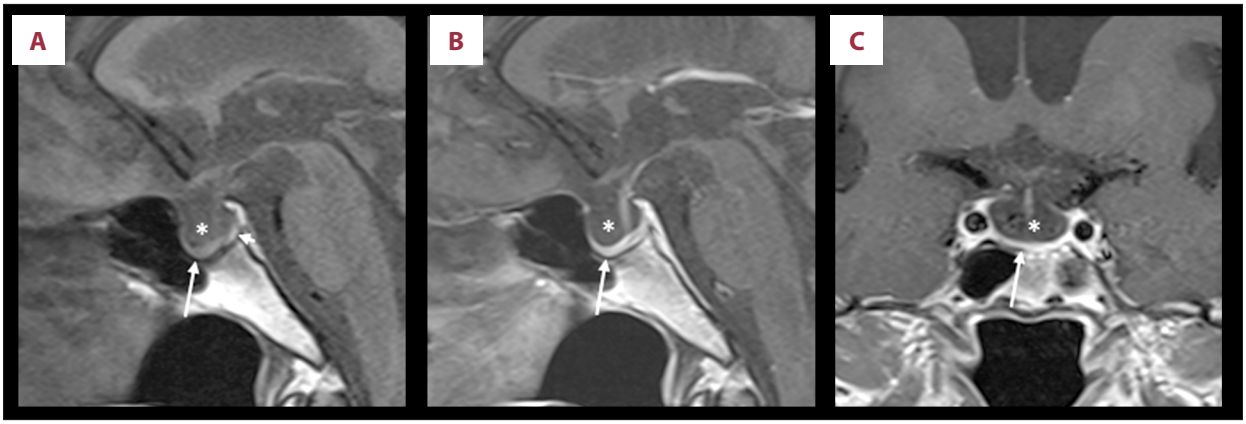

Figure 1. Magnetic resonance imaging of the pituitary gland (September 2018). (**A**) A plain T1-weighted image (sagittal plane) showing that the sella was filled with cerebrospinal fluid (*) and that the pituitary gland was flattened along the sphenoidal bone (long arrow), indicating an empty sella turcica. A normal high-intensity signal was emitted by the posterior pituitary (short arrow). (**B, C**) Gadolinium-enhanced T1-weighted images (**B**, sigittal plane; **C**, coronal plane) showing a normally enhanced hypophysial stalk, a flattened anterior pituitary (long arrow), and the sella filled with cerebrospinal fluid (*).

The patient tested negative for pituitary autoantibody, as well as for thyroid peroxidase autoantibody, thyroglobulin autoantibody, TSH-binding inhibitory immunoglobulin, adrenocortical autoantibody, and anti-nuclear antibody. Human leukocyte antigen typing revealed the presence of A*02: 07/24: 02 and B*40: 01/46: 01 class I genes and DRB1*04: 05/15: 01, DQB1*04: 01/06: 02, and DQA1*01: 02/03: 03 class II genes.

The patient began corticosteroid replacement therapy with oral hydrocortisone (15 mg/day) for IAD on day 6 after transfer. Her anorexia and fatigue resolved within 1 week, and blood pressure was around 120/70 mmHg. The hyponatremia rapidly improved, and oral sodium chloride was discontinued. Blood tests performed on day 12 after transfer showed normal levels of sodium (144 mEq/L), potassium (3.9 mEq/L), chloride (107 mEq/L), and AVP (0.7 pg/mL) for Posm (289 mOsm/kg). The patient was discharged on day 13 after transfer to our hospital.

The patient was followed up at our outpatient clinic. One month after discharge, she had normal serum levels of thyroid hormones (FT_4,1.42 ng/dL; FT_3, 2.89 pg/mL) and TSH (2.57 μIU/mL), indicating that the elevated TSH due to hypocortisolemia [18] resolved after corticosteroid replacement therapy. Her subsequent clinical course during corticosteroid replacement therapy with oral hydrocortisone (15 mg/day) for more than 1 year has been uneventful, with no recurrence of hyponatremia or RM.

Discussion

Table 3 shows the characteristics of reported patients with central AI who exhibited hyponatremia and RM. They presented with symptoms indicative of AI, RM, or hyponatremia, and had varying degrees of low serum sodium and high serum CPK levels. The present patient with a 2-month history of AI symptoms, including anorexia and fatigue, was diagnosed with IAD that manifested as severe hyponatremia and RM after 2 days of vomiting and muscle weakness. To the best of our knowledge, the present case is the first report of hyponatremia and RM in a patient with IAD.

The management of RM includes intravenous fluid infusion and the elimination of causal factors [8–10]. Previously reported central AI patients with hyponatremia and RM, who had coexisting central hypothyroidism, recovered from both hyponatremia and RM within weeks after commencement of hormone replacement therapy with corticosteroids and subsequent levothyroxine [14,15]. In the present case of IAD, RM was resolved with fluid infusion and correction of hyponatremia with sodium chloride administration; however, after reducing the amount of sodium chloride administered, she had unresolved hyponatremia associated with hypocortisolemia and excessive AVP secretion. After the patient was diagnosed with IAD and started on corticosteroid replacement therapy, the hyponatremia rapidly and completely resolved with normalization of AVP levels. These findings indicate that earlier IAD diagnosis and corticosteroid replacement therapy would have resolved both hyponatremia and the associated RM sooner and more effectively in our patient. The present case highlights the importance of considering the possibility of central AI in patients with hyponatremia and inappropriately high plasma AVP levels.

Previously reported patients with primary or central AI who exhibited hyponatremia and RM presented with several factors, in addition to hyponatremia, that could induce RM, such as dehydration [11], hypothyroidism [12,14,15,17], and hypocortisolemia. In the present case, the patient exhibited no clinically

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Table 3. Summary of reported patients with central adrenal insufficiency who exhibited hyponatremia and rhabdomyolysis.

Ref.	Age/ sex	Major symptoms	Serum sodium (mEq/L)	Serum CPK (IU/L)	Acute kidney injury	Pituitary disorder	Central AI	Central hypothyroidism	Radiological findings of the pituitary	Other findings
[12]	58/F	Confusion, myalgia, lower limb weakness	94	>40000	(+)	Sheehan's syndrome	(+)	(+)	N.D.	Hemorrhage of the scapular and gluteal muscles
[14]	66/F	Edema and pain in the legs, hypotension, psychomotor impairment	125	4250	(+)	Hypopituitarism	(+)	(+)	Empty sella	None
[15]	64/F	Fatigue, mental lethargy, myalgia, leg cramp, dysarthria, vomiting	129	1337	(-)	Sheehan's syndrome	(+)	(+)	Atrophy	None
[17]	22/M	Appetite loss, vomiting, edema, muscle weakness and cramps	126	5898	(+)	Hypopituitarism	(+)	(+)	No abnormality	Heart failure
Present case	67/F	Anorexia, fatigue, vomiting, muscle weakness	118	6968	(-)	IAD	(+)	(-)	Empty sella	None

AI – adrenal insufficiency; CPK – creatine phosphokinase; IAD – isolated adrenocorticotropic hormone deficiency; N.D. – not described.

evident dehydration or hypothyroidism when RM developed. Her RM resolved with correction of hyponatremia, despite the presence of hypocortisolemia before corticosteroid replacement therapy for IAD. Thus, hyponatremia was primarily involved in the development of RM in our patient.

Although the causes of RM are diverse, its pathogenesis is thought to follow a common pathway [8–10]. In normal skeletal muscle, the sarcolemma, a thin membrane that encloses striated muscle fibers, has many pumps that regulate the cellular electrochemical gradients, maintaining low levels of intracellular sodium and calcium and a high level of intracellular potassium. These processes require adenosine triphosphate (ATP) as an energy source; any process leading to ATP depletion may result in RM. ATP depletion triggers dysfunction of pumps, such as the sodium-potassium ATPase pump in the sarcolemma and calcium ATPase pump in the sarcoplasm, increases cellular permeability to sodium ions, increasing intracellular calcium concentration, and eventually induces myocyte degradation. The presumed mechanism of hyponatremia-related RM involves sarcolemma disruption due to sodium-potassium ATPase pump dysfunction [9].

The pathogenesis of IAD is not fully understood; however, IAD can be caused by traumatic injury [7], lymphocytic hypophysitis [19], pituitary autoimmunity (often associated with other organ-specific autoimmune disorders) [20], medications [21], or radiation therapy for a brain tumor [22]. In addition, IAD may be associated with primary empty sella [23], which is characterized by the intrasellar herniation of the subarachnoid space that is often associated with variable degrees of flattening of the pituitary gland in patients without previous pituitary pathologies [24]. In the present case, the patient had never experienced a brain tumor, radiation therapy, or traumatic injury, and did not exhibit clinically evident hypophysitis or autoimmunity. Her IAD was associated with primary empty sella.

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Conclusions

We report an unusual case of severe hyponatremia and RM in an elderly patient with IAD. This case highlights the importance of considering the possibility of central AI in patients with hyponatremia and inappropriately high plasma AVP levels. In addition, physicians should be aware that RM associated with hyponatremia can be an unusual but important manifestation of IAD.

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Conflict of interest

None.

Abbreviations

ACTH – adrenocorticotropic hormone; **AI** – adrenal insufficiency; **ATP** – adenosine triphosphate; **AVP** – arginine vasopressin; **CPK** – creatine phosphokinase; **CRH** – corticotropin-releasing hormone; **FT_3** – free triiodothyronine; **FT_4** – free thyroxine; **GHRP-2** – growth hormone-releasing peptide-2; **GRF** – growth hormone-releasing factor; **IAD** – isolated adrenocorticotropic hormone deficiency; **LHRH** – luteinizing hormone-releasing hormone; **Posm** – plasma osmolality; **RM** – rhabdomyolysis; **TRH** – thyrotropin-releasing hormone; **TSH** – thyroid-stimulating hormone

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