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A Case of Transient Hypercortisolism Simultaneously Occurring With the Syndrome of Inappropriate Antidiuretic Hormone Secretion Induced by Olanzapine

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Abstract

We herein present a case of a 71-year-old woman who was referred to our hospital with the prolonged disturbance of consciousness after two convulsive seizures the day before admission. She was in long-term hospitalization because of schizophrenia. Blood tests showed severe low-osmolar hyponatremia (Osm: 226 mOsm/kg and Na: 110.3 mEq/L) and hypokalemia (K: 2.67 mEq/L). An endocrine examination revealed that the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which was induced secondary to olanzapine, and transient hypercortisolism had simultaneously occurred. Low- and high-dose overnight dexamethasone suppression tests and the corticotropin-releasing hormone (CRH) test showed similar endocrine responses to those in patients with Cushing's syndrome. However, no abnormality in the pituitary gland was detected using contrast magnetic resonance imaging (MRI). After admission, elevated adrenocorticotropic hormone (ACTH) and cortisol levels gradually decreased and normalized by the time of discharge. Transient hypercortisolism sometimes occurs in patients with schizophrenia. Hypercortisolism in the present case was considered to be induced by stress such as severe hypo-osmotic hyponatremia and convulsions in addition to the underlying disorder of schizophrenia. Clinicians need to routinely check electrolytes in patients taking olanzapine in order to prevent insidious progression to severe hyponatremia. To the best of our knowledge, this is the first case report in which an endocrine examination and its interpretation were performed for SIADH accompanied by transient hypercortisolism due to the stimulation of ACTH.

Keywords: Hypercortisolism; Syndrome of inappropriate antidiuretic hormone secretion; Olanzapine; Hyponatremia; Hypokalemia

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Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is defined by a disorder of impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH) [1]. SIADH is one of the common causes of hyponatremia, and needs to be considered in a differential diagnosis of patients with hypo-osmotic hyponatremia. The etiology of SIADH is diverse, including CNS disturbances, malignancies, surgery, pulmonary diseases, and drugs, with psychotropic agents such as olanzapine, as reported herein, as a cause of SIADH.

On the other hand, the pathology causing hypercortisolism is diverse. Mild elevations in serum cortisol levels may occur in a severely stressed state (physical or psychological), in patients with severe depressive illnesses, or sometimes in patients with schizophrenia [2]. Furthermore, severe hypercortisolism is a well-known condition caused by the overproduction of cortisol such as Cushing's syndrome [3].

We herein report an extremely rare case of a 71-year-old woman with transient hypercortisolism simultaneously occurring with SIADH induced by olanzapine. We also discuss relevant reports available in the literature.

Case Report

This is the case of a 71-year-old woman who was referred to our hospital with the prolonged disturbance of consciousness after two convulsive seizures lasting approximately 5 s on the day prior to admission. Blood tests in the previous hospital showed severe low-osmolar hyponatremia (Osm: 226 mOsm/kg and N: 110.3 mEq/L) and hypokalemia (K: 2.67 mEq/L). She had a previous history of schizophrenia from the age of 16, and was in the nearby psychiatric hospital from 18 years of age to the day before hospitalization. There was no history of polydipsia or polyuria. She had been administered psychotropic drugs (olanzapine; product name: Zyprexa) at a dose of 5 mg/day and mazaticol hydrochloride hydrate (product name: Pentona) at 4 mg/day to treat schizophrenia for more than 3 years, and her medical condition of hallucinations and delusions had been controlled. A few cases of severe hyponatremia caused by SIADH secondary to the internal use of olanzapine

Table 1. Laboratory Findings on Admission

Urinalysis	
Protein	±
Glucose	-
Ketone bodies	-
Bilirubin	-
Blood cell count	
WBC	15,100/μL
RBC	394×10^4/μL
Hb	11.7 g/dL
Plt	28.2×10^4/μL
Blood chemistry	
T-bil	0.9 mg/dL
AST	30 U/L
ALT	11 U/L
LDH	368 U/L
NH3	79 μg/dL
ALP	163
CK	249 U/L
T-cho	150 mg/dL
TG	43 mg/dL
TP	5.2 g/dL
Alb	2.9 g/dL
BUN	10.2 mg/dL
Cr	0.36 mg/dL
Na	110.3 mEq/L
K	2.67 mEq/L
Cl	67 mEq/L
Ca	7.2 mg/dL
IP	3.0 mg/dL
Mg	1.9 mg/dL
Osm	226 mOsm/kg
Glu	125 mg/dL
HbA1c	5.8%
Serological test	
CRP	0.6 mg/dL
Endocrine examination	
Free T3	1.6 pg/mL
Free T4	1.6 ng/dL
TSH	0.541 μIU/mL
ACTH	122 pg/mL
Cortisol	35.9 μg/dL
PRA	0.2 ng/mL/h
PAC	133 pg/mL
ADH	5.9 pg/mL
Urine test	
Na	68.8 mEq/L
K	47.7 mEq/L
Osm	435 mOsm/kg
Blood gas analysis	
pH	7.555
PCO_2	40 mm Hg
PO_2	113 mm Hg
HCO_3^-	35.4 mEq/L
BE	11.9 mmol/L

PRA: plasma renin activity, ADH: antidiuretic hormone or vasopressin. U-Na and U-K indicate Na and K in the urine, respectively.

have been reported [4]. Since no other apparent cause for the development of SIADH was found, olanzapine was regarded as the causative agent and was discontinued after admission. Since she had no previous history of seizures until this event, convulsive seizures were considered to be induced by severe hyponatremia. Although her convulsions had subsided at the time of admission, her consciousness remained cloudy. Neither anisocoria nor the loss of the light reflex was observed. Head computed tomography showed no findings indicating brain vascular disorders in the acute phase.

On admission, her vital signs were as follows: height, 160 cm; weight, 55.6 kg; body temperature, 37.4 °C; blood pressure, 180/85 mm Hg; heart rate, 85 beats/min; respiratory rate, 15 breaths/min; SpO_2 98% (under the supply of O_2 0.5 L/min through a mask). She did not have any physical features characteristic of Cushing's syndrome such as a moon face, buffalo hump, central obesity with a protruding abdomen, and thin extremities. She did not gain or lose weight during the year prior to her hospitalization.

Since blood tests on admission showed severe hyponatremia (Na: 110.3 mEq/L) and hypokalemia (K: 2.67 mEq/L), an endocrine examination was performed in the morning of the day after her hospitalization (Table 1).

The SIADH is defined by a disorder of impaired water excretion caused by the inability to suppress the secretion of ADH. According to the diagnostic criteria of SIADH by the Japanese Ministry of Health, Labor, and Welfare [5], urine sodium concentrations are typically greater than 20 mEq/L, serum potassium concentrations are normal, there is no acid-base disturbance, and serum uric acid concentrations are frequently low. In the present case, since the laboratory examination showed low-osmolar hyponatremia (Osm: 226 mOsm/kg and Na: 110.3 mEq/L), elevated urinary sodium (68.8 mmol/L), and an inappropriate elevation in ADH, a diagnosis of SIADH was made.

Serum adrenocorticotropic hormone (ACTH) (122 pg/mL) and cortisol (35.9 μg/dL) levels were elevated in the early morning of the day after her hospitalization (Table 1). Her urinary free cortisol level was elevated to 655 μg/day (normal range: 11.2 - 80.3) on the sixth day (Table 2).

Table 2. Urinary Cortisol in 24-H Urine Collection, and Diurnal Variations in Plasma ACTH and Serum Cortisol

	Sixth day		34th day	
	8:00	23:00	8:00	23:00
ACTH (pg/mL)	66.9	44.4	19.3	2.1
Cortisol (μg/dL)	23.0	16.0	12.5	4.7
Urinary cortisol (μg/day) (11.2 - 80.3)	655		96.6	

Her urine was collected and stored in 24-h collection containers for the measurement of urinary cortisol levels.

Her plasma ACTH level and serum cortisol level at 8:00 on the sixth day were 66.9 pg/mL (normal range: 7.2 - 63.3) and 23.0 μg/dL (normal range: 4.0 - 19.3), respectively (Table 2). Late in the evening (23:00) on the same day, her plasma ACTH level and serum cortisol level were 44.4 pg/mL and 16.0 μg/dL, respectively. Healthy people typically exhibit diurnal variations in serum cortisol levels, namely, high in the morning and low in the night. Her serum cortisol levels were considered to be high in the early morning as well as late in the evening. This result indicated that diurnal variations in serum cortisol levels had almost disappeared on the sixth day. On the 34th day, her serum cortisol level became normal in the early morning and decreased late in the evening (Table 2). The normalization of cortisol levels in the early morning and the appearance of normal physiological diurnal variations on the 34th day indicated that her hypercortisolism was transient.

The excess secretion of cortisol in patients with Cushing's syndrome frequently causes a decrease in serum potassium levels due to its excretion of through the mineralocorticoid actions of cortisol. Therefore, since Cushing's syndrome was suspected as a pre-existing comorbid illness, an overnight low-dose (0.5 mg) dexamethasone suppression test (DST) was performed on the 10th day (Table 3). After administrating 0.5 mg of dexamethasone late in the evening (23:00), blood collection for ACTH and cortisol was performed at 8:00 the next day. The serum cortisol level at 8:00, which is typically suppressed at 5 μg/dL or less in healthy subjects, was 18.7 μg/dL (higher than 5 μg/dL). A high-dose (8 mg) overnight DST was performed on the 14th day (Table 3). The serum cortisol level at 8:00 the next morning after administrating an 8-mg dose of dexamethasone late in the evening (23:00) was 3.1 μg/dL and was suppressed to less than half the cortisol level in the early morning at the time of admission. The corticotropin-releasing hormone (CRH) test showed that the apical value of plasma ACTH was more than 1.5-fold higher than the previous value (Table 4). Since the results of these load tests suggested ACTH-dependent Cushing's syndrome, a search for pituitary adenomas was performed. Brain computed tomography showed that the pituitary fossa was within normal limits. Furthermore, contrast-enhanced magnetic resonance imaging (MRI) of the pituitary gland did not detect any pituitary adenoma.

Table 3. Low- and High-Dose Dexamethasone Suppression Tests

	8:00
Overnight 0.5 mg test on the 10th day	
ACTH (pg/mL)	25.9
Cortisol (μg/dL)	18.7
Overnight 8 mg test on the 14th day	
ACTH (pg/mL)	2.1
Cortisol (μg/dL)	3.1

Low-dose overnight DST: 1 mg of dexamethasone was taken orally at 23:00, and her blood was drawn at 8:00 on the next day for plasma ACTH and serum cortisol measurements. High-dose overnight DST: 8 mg of dexamethasone was taken orally at 23:00, and her blood was drawn at 8:00 on the next day for plasma ACTH and serum cortisol measurements.

Olanzapine was suspected as the causative agent because no other apparent cause of SIADH was found. The administration of olanzapine was discontinued after admission and liquid intake was restricted as the treatment for SIADH. The correction of the electrolyte abnormality was initially performed using a drip and then orally. Hyponatremia normalized on the 21st day, while hypokalemia normalized on the 41st day. She subsequently continued to maintain normal serum levels of sodium and potassium.

On the 41st day, her psychotic symptoms and mood had markedly improved, and she was transferred to her former psychiatric hospital with medication: risperidone at a dose of 1 mg/day after dinner and flunitrazepam at 1 mg/day at bedtime.

Discussion

Mild elevations in serum cortisol levels have been reported to occur in a severely stressed state (physical or psychological)

Table 4. Corticotropin-Releasing Hormone Stimulation Test

	0 min	15 min	30 min	60 min	90 min	120 min
ACTH (pg/mL)	24.2	77.1	88.6*	71.8	39.7	29.3
Cortisol (μg/dL)	16.0	23.7	27.2	29.3*	23.0	20.5

Human CRH (Corticorelin; hCRH "TANABE") at 100 μg was injected as an intravenous bolus. Blood samples for ACTH and cortisol were drawn 0, 15, 30, 60, 90, and 120 min after the CRH injection. The CRH test revealed an increase in plasma ACTH and cortisol levels. An elevation in ACTH occurred after 15 - 60 min and the highest level was reached 30 min after the CRH injection, while plasma cortisol levels peaked 60 min after the CRH injection. The plasma ACTH peak value (88.6 pg/mL at 30 min) was more than 1.5-fold higher than the previous value (24.2 pg/mL). Similar endocrine responses to those observed in patients with pituitary-dependent Cushing's syndrome were noted. * indicates the top value.

or in patients with severe depressive illnesses. These clinical conditions are considered to be transiently appropriate stress reactions and revert to normal serum cortisol levels when stress conditions are resolved. Cushing's syndrome and the excessive use of cortisol are a clinically significant disease and condition, respectively, accompanied by severe hypercortisolism.

Previous studies reported that schizophrenia patients had significantly elevated serum cortisol levels. Its pathogenesis is considered to be associated with abnormal activity by the hypothalamic-pituitary-adrenal (HPA) axis. In addition, antipsychotic treatments for schizophrenia patients with hypercortisolism have been suggested to reduce high serum cortisol levels to within normal limits [6-8].

A non-suppression reaction to DST may occur in patients with schizophrenia. As discussed, the results of the overnight DST and CRH tests in this case were similar to those of endocrine tests for Cushing's syndrome. Mann et al reported that a treatment with olanzapine for approximately 4 weeks in patients with schizophrenia resulted in reduced HPA activity, which, in turn, led to lower plasma cortisol levels than cortisol levels prior to the treatment. The mechanisms responsible for the decrease in HPA activity may involve antagonistic effects at the D2 and 5-HT2 receptors of olanzapine [8].

Venkatasubramanian et al found that schizophrenia patients had significantly lower serum insulin-like growth factor-1 (IGF-1) levels and higher serum cortisol levels than healthy controls at baseline, and IGF-1 levels increased, whereas cortisol levels decreased after an antipsychotic treatment. Decreased serum IGF-1 levels were considered to be strongly associated with the neurodevelopmental pathogenesis of schizophrenia [6, 7]. In the present case, although her serum IGF-1 level was not examined during hospitalization, her elevated cortisol level at the time of admission improved to within normal ranges on the 34th day.

Cushing's syndrome presents with a number of symptoms. Although mental symptoms such as depression, mood dysregulation, sleep disturbance, and cognitive abnormalities may be present, they are not specific to Cushing's syndrome [9]. Therefore, since difficulties are associated with identifying patients with Cushing's syndrome from psychiatric symptoms, particularly in the elderly with mental disorders, these patients need to be carefully observed and managed appropriately.

Although our case lacked physical findings characteristic of Cushing's syndrome, she had transient hypercortisolism, the lack of diurnal variations in serum cortisol levels, and reactions similar to Cushing's syndrome in the DST and CRH tests. Therefore, concomitant Cushing's syndrome was suspected in the initial period of hospitalization; however, we were able to reject this possibility based on the improvements observed in abnormal electrolytes and the decrease in serum cortisol levels during the follow-up.

In the present case, transient hypercortisolism was considered to be induced by stress such as severe hypo-osmotic hyponatremia and convulsions in addition to the underlying disorder of schizophrenia.

Psychogenic polydipsia needs to be considered as a possible cause of hyponatremia in the present case because it occurs in between 6% and 20% of psychiatric patients and is more likely to be observed with schizophrenia [10]. Since the present case did not exhibit a noticeable thirst or polyuria, a differential diagnosis of psychogenic polydipsia was excluded.

The etiology of SIADH is diverse, is frequently difficult to specify, and remains unknown. Although some psychotropic drugs are associated with hyponatremia, the exact prevalence of hyponatremia induced by these drugs as an adverse event is currently unclear [11]. Psychotropic drugs such as chlorpromazine, carbamazepine (or a derivative), and selective serotonin reuptake inhibitors, may enhance the release of ADH or increase sensitivity to ADH, and, as a result, lead to SIADH [12].

There are a few reports of SIADH induced secondary to olanzapine, which was used in our case until hospitalization [4, 13]. In the case report by Dudeja et al, their patient with mixed bipolar affective disorder and schizoid personality disorder suddenly developed SIADH after taking olanzapine at 20 mg/day for 2 years [4]. In the case report by Bakhla et al, their patient with recurrent depressive disorder developed SIADH shortly after starting olanzapine at 5 mg/day [13]. The present case had used olanzapine at 5 mg/day for more than 3 years until hospitalization. Based on these case reports, although hyponatremia induced by psychotropic drugs is typically more frequently diagnosed in the first week of treatment, the period and dose of internal use are not considered to be related to the induction of SIADH by olanzapine. Therefore, the judgment of whether olanzapine is the true causative agent of SIADH needs to be considered based on the absence of other causative agents, the recovery of electrolytes after the discontinuation of the drug, and no recurrence thereafter.

In this case, drug-induced hypo-osmotic hyponatremia improved without any recurrence following the discontinuation of olanzapine, a drip treatment with hypertonic or isotonic saline, and the restriction of fluid intake. Olanzapine is considered to be the most probable causative agent because no other apparent cause of SIADH was identified.

Conclusion

An endocrine examination of hypo-osmotic hyponatremia and hypokalemia, which were observed simultaneously at the time of admission, revealed that SIADH, which was induced secondary to olanzapine, and transient hypercortisolism had simultaneously occurred. Hypercortisolism was considered to be induced by stress such as severe hypo-osmotic hyponatremia and convulsions in addition to the underlying disorder of schizophrenia. Clinicians need to routinely check electrolytes in patients taking olanzapine in order to prevent insidious progression to severe hyponatremia. To the best of our knowledge, this is the first case report in which an endocrine examination and its interpretation were performed for SIADH accompanied by transient hypercortisolism due to the stimulation of ACTH.

Consent

Written informed consent was obtained from the patient for the

publication of this case report.

Conflicts of Interest

The authors declare no relevant interest.

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