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Case Report

Circulating Neuroactive Steroid Levels in a Patient With Schizophrenia Who Showed Periodic Catatonia

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Abstract

Catatonia is an abnormal psychological and behavioral state related to stress. The treatment strategy suggests the involvement of neuroactive steroids in its pathophysiology. We report a hospitalized patient with schizophrenia in whom a catatonic state occurred 7 times in 5.5 years. Blood levels of steroid hormones and adrenocorticotropic hormone (ACTH) were measured during the catatonic state and in the intervals between catatonic states (non-catatonic states). Cortisol and dehydroepiandrosterone sulfate (DHEAS) were significantly higher during catatonia than in the non-catatonic state. Cortisol significantly correlated with the ACTH level, whereas blood DHEAS and progesterone correlated only during the non-catatonic state. In addition, the cortisol to DHEAS ratios did not differ between catatonic and non-catatonic states. Although the correlating elevations of ACTH and cortisol implied activation of the hypothalamic-pituitary-adrenal axis (HPA-axis) in the catatonic state, DHEAS levels did not seem to increase in a manner dependent on the HPA-axis or the production of progesterone. The results suggest that the catatonic state was a neuroendocrinological state of HPA-axis activation with comparable increases in DHEAS levels.

Key Words: catatonia, HPA-axis, neuroactive steroids, DHEAS, cortisol, stress

Abbreviations: ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; GABA, γ-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; NMDA, N-methyl-D-aspartate.

Introduction

Many mental diseases are related to neuroendocrinological responses to stress that are exerted by the hypothalamic-pituitary-adrenal (HPA) axis. In this system, adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to release glucocorticoids, mainly cortisol in humans [1]. Dehydroepiandrosterone (DHEA) and its sulfated form, DHEAS, are also secreted from the adrenal cortex in response to stress [1]. DHEA is a weak androgen and a precursor of more potent androgens, such as testosterone, and aromatized steroids, such as estrogens [2]. DHEAS exists abundantly in the circulation and works as a pool for steroid hormones [2]. DHEA and DHEAS are often discussed indiscriminately regarding their biological functions, such as DHEA(S), because they can be converted into each other in the presence of bioactive enzymes [2]. For example, DHEA(S) is considered to work to ameliorate the adverse effects of sustained elevation of glucocorticoids under stress [2]. DHEA(S) is also a neuroactive steroid and can interact with N-methyl-D-aspartate (NMDA), γ-aminobutyric acid (GABA)-A, and sigma receptors [2]. A correlation between blood and cerebrospinal fluid levels of DHEA and DHEAS has been demonstrated. Circulating DHEA(S) can be transferred to the brain, but DHEA(S) can also be synthesized de novo in glial cells and neurons [2]. Because of their anti-stress and neuroactive properties, DHEA(S) levels in the blood and their ratios to cortisol levels have been investigated in mental diseases, including schizophrenia, depression, and posttraumatic stress disorder, and in situations of psychological stress [1, 3].

Catatonia is a pathological mental and behavioral state characterized by hypokinesis, mutism, or negativism. This syndrome can be associated with diverse psychiatric and somatic diseases [4] and pathological psychological states [5]. Benzodiazepines and NMDA receptor antagonists are effective for the treatment of catatonia, suggesting an involvement of GABA-A or NMDA receptor systems in this state [4]. Therefore, activity of the HPA-axis, including the secretion of DHEA(S), may be related to the pathophysiology of catatonia.

To our knowledge, no systemic studies have been conducted on stress-related hormones or neuroactive steroids, including DHEA(S) and progesterone, in catatonia, although they have been studied in schizophrenia. We had an opportunity to evaluate the circulating levels of ACTH, cortisol, DHEAS, and progesterone in periodically observed catatonic states in a patient with schizophrenia.

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Case Presentation

The patient was a 73-year-old woman. She became a factory worker after 9 years of education. Insomnia and refusal, including refusal to eat, appeared first, at age 19 years. Her symptoms were diagnosed as negativism and catalepsy, and she was admitted and treated with electroconvulsive therapy. Persecutory delusions emerged when she was 23 years old, such as others telling her rumors and being vilified in the neighborhood, and she was admitted again. After being discharged, she worked as a charwoman, married, and gave birth to a child. After that, her psychiatric symptoms recurred and she needed to be hospitalized when the following events occurred: her divorce, her second marriage, her son's car accident, her mother's hospitalization, and the deaths of her mother, friends, and relatives. She started to live with her son at the age of 53 years. After surgery for breast cancer at 65 years old, she lived alone, receiving welfare services. She was hospitalized at 68 years of age because of worsening symptoms. During her 5.5 years of hospitalization, recurrences of catatonia were observed every 2 to 3 months, at 7 time points in total between the ages of 68 and 73 years. During her catatonic states, she was silent and displayed akinesia and refusal, including refusal to eat. Tube feeding or bodily fixation were often required to sustain her life. When catatonia was not present (hereafter, non-catatonic states), she was able to eat, talk, walk, and take care of herself. When her catatonic and non-catatonic states were evaluated with the 14-item Bush-Francis catatonia rating scale, she scored ≥27 points and ≤3 points, respectively.

Diagnostic Assessment

Endocrinological measures were obtained from blood tests that were performed to assess the patient's general condition, physical complications, or endocrinological abnormalities. Examinations, including the assay of ACTH, cortisol, DHEAS, or progesterone, were performed 28 times in total: 15 times during catatonic states and 13 times during non-catatonic states. Blood was collected at 10 AM. ACTH, cortisol, DHEAS, and progesterone were assayed by SRL, Inc. (Tokyo) using an electrochemiluminescence immunoassay for the assay of ACTH, cortisol, and progesterone and a chemiluminescent enzyme immunoassay for the assay of DHEAS. The ratio of cortisol and DHEAS in blood was calculated for comparisons with previous results in pathological mental states [3]. Differences in the blood levels of ACTH, cortisol, DHEAS, and progesterone were analyzed between catatonic and non-catatonic states by Student *t* tests. Correlations between values obtained from identical blood samples were examined by Pearson's correlation tests separately in catatonic and non-catatonic states. Statistical analyses were performed using PRISM, ver. 5.0c (GraphPad, CA, USA). $P < 0.05$ was considered significant.

Outcome and Follow-up

Blood levels of cortisol and DHEAS significantly increased during the patient's catatonic states compared with her non-catatonic states, although blood levels of ACTH and progesterone did not differ between these states (Fig. 1). We found no significant difference in the DHEAS to cortisol ratio between catatonic and non-catatonic states (means ± SEM 2.25 ± 0.27 and 2.91 ± 0.43, respectively; $n = 15$ and 13, respectively). We found significant positive correlations between ACTH and cortisol levels in both the catatonic and non-catatonic state (Tables 1 and 2). A significant positive correlation between DHEAS and progesterone levels was found in the non-catatonic state (Table 1) but not the catatonic state (Table 2). We found no significant correlations between ACTH and DHEAS, ACTH and progesterone, cortisol and DHEAS, or cortisol and progesterone in either the non-catatonic (Table 1) or catatonic state (Table 2).

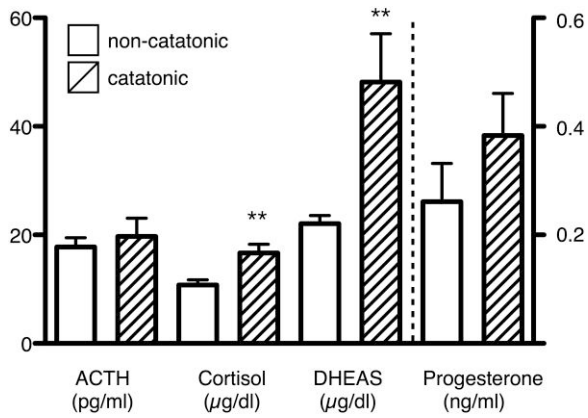

Figure 1. Blood levels of ACTH (pg/mL), cortisol (μg/dL), DHEAS (μg/dL), and progesterone (ng/mL) during catatonic and non-catatonic states. Data are presented as means with SEM (error bars). Open columns: non-catatonic state; hatched columns: catatonic state. ACTH, $n = 12$ and 15 samples in non-catatonic and catatonic states, respectively. Cortisol and DHEAS, $n = 13$ and 15 in non-catatonic and catatonic states, respectively. Progesterone, $n = 12$ and 13 in non-catatonic and catatonic states, respectively. $^{**}P < 0.01$, Student *t* tests, non-catatonic vs catatonic.

Table 1. Pearson *r* in correlations between ACTH, cortisol, DHEAS, and progesterone in the non-catatonic state

	ACTH	Cortisol	DHEAS	Progesterone
ACTH		0.7380**	0.1115	0.4263
Cortisol			0.3060	0.3140
DHEAS				0.6773*

* $P < 0.05$, ** $P < 0.01$

Table 2. Pearson *r* in correlations between ACTH, cortisol, DHEAS, and progesterone in the catatonic state

	ACTH	Cortisol	DHEAS	Progesterone
ACTH		0.7846**	0.2489	0.1207
Cortisol			0.4705	0.3939
DHEAS				0.5488

** $P < 0.01$

Discussion

In the history of this case, catatonic episodes seemed to occur in relation to life events, such as marriage, divorce, a car accident, and illnesses or deaths of family or friends, suggesting that catatonia was triggered by life events, especially stressful

ones. In this study, recurrence of catatonia was observed during a period of hospitalization in what is considered a stable environment. Thus, catatonia and recovery appeared to occur spontaneously or independent of life events.

In the observation of this case, blood levels of cortisol and DHEAS increased during catatonic states compared to non-catatonic states, whereas blood levels of ACTH and progesterone did not differ between non-catatonic and catatonic states. Positive correlations between ACTH and cortisol levels were found in both the catatonic and non-catatonic states, suggesting that these concomitant changes in ACTH and cortisol indicate HPA-axis activity. Therefore, the HPA-axis appears to be activated in catatonia, but blood tests at a single time point may not be sufficient to detect changes in blood ACTH accompanying stress-related psychosomatic conditions. DHEAS levels did not significantly correlate with ACTH levels. Although some reports have indicated that stress increases blood DHEAS levels, as well as DHEA levels, changes in DHEAS levels may be less sensitive to ACTH than changes in DHEA levels because of a large pool of DHEAS in the circulation [1]. Other, more profound factors may be involved in the dynamics of circulating DHEA(S) and the adrenal steroidal metabolism because the administration of DHEA has been reported to decrease cortisol levels and influence the adrenal response to ACTH in postmenopausal women [6]. Furthermore, our results showed a correlation between DHEAS and progesterone levels only in the non-catatonic state but not in the catatonic state. The fact that progesterone is produced in the adrenal cortex at this patient's age and that DHEA supplementation increases progesterone levels in males [7] suggests that the conversion of DHEA to progesterone occurs. Therefore, it is speculated that changes in DHEA metabolism in the catatonic state, such as the conversion rate between DHEAS and DHEA, alter the secretion of progesterone. Further studies are needed to clarify the involvement of progesterone and the relationship between progesterone and DHEA(S) in catatonia.

The DHEAS to cortisol ratios did not differ between the patient's catatonic and non-catatonic states, indicating an elevation of DHEAS comparable to the increase in cortisol. The DHEAS to cortisol ratio being independent of the clinical state is consistent with a previous finding that the DHEAS to cortisol ratio is related to individuals' psychological traits rather than clinical states [3]. Increases in DHEA(S) and the DHEA(S):cortisol ratios appear to be indicators of favorable prognosis and mild symptoms in schizophrenia [3]. In recent reports, higher blood DHEAS levels correlated with lower aggression [8], and cortisol to DHEA ratios correlated with hippocampal and prefrontal cortex volume loss [9]. In addition, higher levels of DHEAS have been found in patients with first-episode psychosis, which suggests functional physical responses [10].

In conclusion, our observations suggest that catatonia is characterized by increased cortisol levels due to an activated HPA-axis and comparable elevation of DHEAS. Given that increased DHEAS antagonizes the adverse events associated with elevated cortisol, it is possible that a favorable and protective response in adrenal steroid metabolism occurs during catatonia. Furthermore, considering its neuroactive properties, the changes in DHEA(S) levels may be involved in neuronal mechanisms underlying the development of catatonia through interaction with NMDA, GABA-A, or sigma receptors.

Learning Points

- The hypothalamic-pituitary-adrenal axis is activated in catatonia.
- Blood concentrations of both cortisol and DHEAS are high during catatonia.
- Elevated DHEAS may antagonize adverse events in hypercortisolism in catatonic states.
- As a neuroactive steroid, DHEAS may be involved in the development of catatonia.
- Simultaneous measurement of cortisol and DHEAS in blood, even at a single time point, is useful for assessing psychosomatic states, including catatonia.

Contributors

All authors were involved in the diagnosis and management of this patient and manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

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

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