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Clinical investigation of a unique type of hypothalamic adrenal insufficiency

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Abstract

Hypothalamic adrenal insufficiency (AI) is a rare but distinct type of AI. The leading cause of hypothalamic AI is a secondary side-effect of exogenous steroid intake, particularly in large amounts and/or long-term periods. The next cause would be the effect of the tumor in the hypothalamic lesions. We show here 9 cases of hypothalamic AI without any disorder on imagings and a history of steroid administration. All patients had general fatigue; 7 patients (77.8%) had a history of hypoglycemia; 5 patients (55.6%) had a history of hypotension. None of the patients had hyponatremia, hyperkalemia, or eosinophilia. Their morning plasma adrenocorticotropic hormone (ACTH) value was low at 8.5 ± 4.2 pg/mL, and serum cortisol value was low at 4.5 ± 1.3 μg/dL. All patients demonstrated normal responses during the corticotropin-releasing hormone loading (CRH) test but inadequate responses during the insulin tolerance test (ITT). After hydrocortisone replacement therapy, their morning plasma ACTH and serum cortisol values were significantly recovered ($P < .05$). Moreover, more than half of the patients were fine after discontinuing hydrocortisone replacement therapy. These results indicate that this unique type of hypothalamic AI has a curable clinical course making hydrocortisone replacement therapy a novel therapeutic option.

Abbreviations: ACTH = adrenocorticotropic hormone, AI = adrenal insufficiency, CRH = corticotropin-releasing hormone, ihAI = idiopathic hypothalamic AI, ITT = insulin tolerance test.

Keywords: adrenal insufficiency, hydrocortisone replacement therapy, hypothalamic disorder

1. Introduction

Adrenal insufficiency (AI) is a hormonal disorder due to impaired cortisol secretion and could cause various symptoms such as fatigue, hypoglycemia, hypotension, weakness, abdominal pain, anorexia, and weight loss.[1–4] Furthermore, AI could develop life-threatening conditions.[5] AI is classed into primary AI (due to adrenal disorder), secondary AI (due to pituitary disorder), or AI due to hypothalamic disorders.[3]

Compared to primary and secondary AI, AI due to hypothalamic disorder is not common. Moreover, hypothalamic AI without any disorder on imagings or a previous history of exogenous steroid administration is quite rare.

Here, we demonstrate investigations of hypothalamic AI without any disorder on imagings or exogenous steroid intake with a clinical course.

2. Materials and Methods

2.1. Ethical approval of the study protocol

The study protocol was approved by the Ethics Review Committees of Fukuoka University (Fukuoka, Japan). Written informed consent was obtained from the patients for participation in the study. The study was carried out according to the principles of the Helsinki Declaration.

2.2. Study participants

We investigated 9 individuals with hypothalamic AI without any disorder on imagings or exogenous steroid intake at Fukuoka University Chikushi Hospital from April 2014 to September 2017. All patients underwent magnetic resonance imaging, and there were no disorders in the hypothalamic lesions. Besides, we confirmed that all patients did not have a previous history of exogenous steroid administration against any disease.

2.3. Methods

We collected data on age, sex, body mass index, clinical symptoms, laboratory tests for all patients at diagnosis of hypothalamic AI without any disorder on imagings or exogenous steroid intake.

KT and IA contributed equally to this work.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Hypotension was defined as having a history of systolic blood pressure <80 mm Hg with related symptoms such as vertigo.[6–8] Hypoglycemia was defined as any combination of having a history of random glucose <60 mg/dL or having a history of random glucose <70 mg/dL with related symptoms such as shivering.[6,9] Hyponatremia was defined as the serum sodium value <135 nmol/L.[9,10] Hyperkalemia was defined as the serum potassium value >5.0 nmol/L.[11] Eosinophilia was defined as eosinophils was >5.0% in all white blood cells.[6,12]

Adrenal crisis was defined as acute impairment of the general condition requiring hospital admission and intravenous glucocorticoid administration with symptoms such as disturbance of consciousness, severe fatigue hypotension, hypoglycemia, and hypovolemia.[5,13,14]

Hypothalamic AI was diagnosed with the combination of the following criteria: low morning plasma adrenocorticotropic hormone (ACTH) and serum cortisol value; normal response of plasma ACTH during corticotropin-releasing hormone (CRH) loading test (100 μg injection of human CRH, human CRH, Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan); inadequate response of serum cortisol during insulin tolerance test (ITT) (injection of regular insulin: 0.1 unit/kg body weight). Normal response of CRH loading test was defined as; peak ACTH value >50 pg/mL or 2-fold increase from baseline, peak serum cortisol value <18 μg/dL or 2-fold increase from baseline.[9,15–17] Inadequate response of serum cortisol after ITT was defined as: peak serum cortisol value <18 μg/dL and/or delayed cortisol response after adequate hypoglycemia (more than 30 minutes after plasma glucose value <50 mg/dL) according to previous reports.[6,9]

After diagnosis, all patients received hydrocortisone replacement therapy (5–10 mg/day). Then, we measured patients' morning plasma ACTH and serum cortisol value every 2 to 4 months and investigated and analyzed the changes in patients' morning plasma ACTH and serum cortisol value before and after hydrocortisone replacement therapy. Furthermore, we also investigated and analyzed the relationship between improvement in morning plasma ACTH or serum cortisol value and the following parameters: age, sex, body mass index, and morning plasma ACTH or serum cortisol value at diagnosis.

Table 1

Clinical characteristics of patients.

	n = 9
Age (yr)	30.8 ± 10.2
Male/female	2/7
Body mass index (kg/m^2)	21.4 ± 4.6
Systolic blood pressure (mm Hg)	111.3 ± 14.0
Diastolic blood pressure (mm Hg)	68.7 ± 12.6
Symptoms	
General fatigue	9 (100%)
Hypoglycemia	7 (77.8%)
Hypotension	5 (55.6%)
Hyponatremia	0 (0.0%)
Hyperkalemia	0 (0.0%)
Eosinophilia	1 (11.1%)
History of adrenal crisis	4 (44.4%)
Morning plasma ACTH value (pg/mL)	8.5 ± 4.2
Morning serum cortisol value (μg/dL)	4.5 ± 1.3
Background	
Excessive psychological stress	6 (66.7%)
Continuous pain of trigeminal nerve	1 (11.1%)
Depression	2 (22.2%)

Data are shown as mean ± standard deviation.
ACTH = adrenocorticotropic hormone.

Table 2

Details of baseline ACTH/cortisol values and the results of and CRH loading test.

Patient	Baseline ACTH value (pg/mL)	Baseline cortisol value (μg/dL)	ACTH value 15 min after CRH injection (pg/mL)	ACTH value 30 min after CRH injection (pg/mL)	ACTH value 60 min after CRH injection (pg/mL)	Cortisol value 15 min after CRH injection (μg/dL)	Cortisol value 30 min after CRH injection (μg/dL)	Cortisol value 60 min after CRH injection (μg/dL)
1	10.3	5.6	52.0	53.6*	52.3	17.6	18.7*	17.5
2	2.9	5.4	61.6*	59.1	34.5	22.6	25.1*	22.4
3	9.3	3.0	27.5	38.0*	21.0	16.7	22.7*	20.7
4	5.3	5.3	39.9	49.2*	43.5	17.5	20.4	22.7*
5	9.3	4.9	38.4	42.7*	32.7	10.0	12.8	14.4*
6	2.0	1.4	10.3	13.4	16.7*	1.5	3.4	5.4*
7	13.4	4.4	245.0*	128.0	58.9	16.8	17.3*	15.1
8	8.7	5.1	34.1	55.5*	38.5	16.5	17.4*	18.1
9	15.3	5.6	94.0*	66.6	58.1	12.0	14.3	16.4*

ACTH = adrenocorticotropic hormone, CRH = corticotropin-releasing hormone.
*Peak value on CRH loading test.

Table 3

Details of the results of insulin tolerance test.

Patient	Most declined glucose value after insulin injection (mg/dL)	Time of hypoglycemia after insulin injection (min)	Cortisol value 15 min after hypoglycemia (μg/dL)	Cortisol value 30 min after hypoglycemia (μg/dL)	Peak cortisol value after hypoglycemia (μg/dL)	Time of peak of cortisol after hypoglycemia (min)
1	23	20	14.1	15.8	26.1	40
2	28	25	6.9	12.9	28.6	65
3	29	20	11.3	14.4	22.2	40
4	39	20	12.0	14.5	23.0	35
5	43	20	10.3	10.1	10.7	40
6	36	30	2.4	2.4	14.6	45
7	48	20	2.4	3.5	4.7	40
8	29	25	7.3	8.6	16.8	35
9	30	25	8.4	8.5	14.8	35

2.4. Statistical analyses

Data are shown as mean ± standard deviation. Statistical analyses were performed using Stata SE version 16 (StataCorp.2019. Stata Statistical Software: Release 16. College Station, TX: Stata Corp LLC.). The Student *t* test estimated the significance of differences between mean values. The relationship was examined using univariate regression analysis. $P < .05$ was considered significant.

3. Results

Table 1 shows the clinical characteristics of the 9 patients in the study cohort. Their mean age was 30.8 ± 10.2 years. Two patients (22.2%) were men, and 5 patients (77.8%) were women. All patients underwent a detailed physical examination. All patients had general fatigue, 7 patients (77.8%) had a history of hypoglycemia, 5 patients (55.6%) had a history of hypotension. No patient had hyponatremia, hyperkalemia, and eosinophilia, which were considered the typical AI symptoms. Regarding the background of patients, 6 (66.7%) had excessive psychological stress, 1 patient (11.1%) had continuous pain of the trigeminal nerve, and 2 patients (22.2%) had depression. Nevertheless, all patients satisfied the criteria of hypothalamic AI, and they did not have any disorder on imagings and history of exogenous steroid administration. Morning plasma ACTH value was 8.5 ± 4.2 pg/mL and morning serum cortisol value was 4.5 ± 1.3 μg/dL. All patients satisfied the normal response for CRH loading test of all patients (Table 2). For the results of ITT, the peak serum cortisol values were less than 18 μg/dL in 5 patients, and the peak values of cortisol after hypoglycemia were more than 30 minutes in all patients (Table 3). After hydrocortisone replacement therapy, morning plasma ACTH and serum cortisol values of all patients were improved during the observation period (Table 4). Nevertheless, all symptoms related to AI improved in all patients. Furthermore, there were significant differences in morning plasma ACTH and serum cortisol values between before and after hydrocortisone replacement therapy ($P < .05$, respectively). Even 5 patients (55.6%) could discontinue hydrocortisone replacement therapy without exacerbating symptoms (Table 5). As for the relationship between improvement in morning plasma ACTH or serum cortisol value with considerable parameters, univariate regression analysis showed no significant relationships with all parameters. However, body mass index did show a tendency of the negative association with improvement in morning serum cortisol value but was not significant ($P = .083$) (Table 6).

4. Discussion

In the present study, we investigated hypothalamic AI without any disorder on imagings or exogenous steroid intake (idiopathic hypothalamic AI, ihAI). Compared to primary AI (due to adrenal disorder) and secondary AI (due to pituitary disorder), hypothalamic AI is rare.[3,6] The leading cause of hypothalamic AI is the administration of exogenous steroids, particularly in large amounts and/or a long-term period.[3] In addition, the next cause of hypothalamic AI would be the effect of the tumor in the hypothalamic lesions.[3,4] However, our subjects did not have any disorder on imagings and history of exogenous steroid administration. Most of the patients had a history of excess psychological stress. Besides, the remaining patients had continuous pain of the trigeminal nerve or depression. The previous study showed that chronic psychological stress could contribute to a decreased cortisol response in the animal model.[18] A recent clinical study also showed that the symptoms of the mental illness of the patients with hypothalamic AI improved by hydrocortisone replacement therapy although morning plasma ACTH

Table 4

Details of changes of ACTH and cortisol values before and after hydrocortisone replacement therapy.

Patient	ACTH value before hydrocortisone replacement therapy (μg/dL)	Cortisol value before hydrocortisone replacement therapy (μg/dL)	ACTH value 12 mo after beginning hydrocortisone replacement therapy (μg/dL)	Cortisol value 12 mo after beginning hydrocortisone replacement therapy (μg/dL)	ACTH value 24 mo after beginning hydrocortisone replacement therapy (μg/dL)	Cortisol value 24 mo after beginning hydrocortisone replacement therapy (μg/dL)	ACTH value 48 mo after beginning hydrocortisone replacement therapy (μg/dL)	Cortisol value 48 mo after beginning hydrocortisone replacement therapy (μg/dL)	ACTH value after hydrocortisone replacement therapy (at the end of observation) (μg/dL)	Cortisol value after hydrocortisone replacement therapy (at the end of observation) (μg/dL)	Observation period (mo)
1	10.3	5.6	12.6	6.35	17.9	10.5	27.9	11.7	35.7	11.9	60
2	2.9	5.4	13.5	9.09	18.4	11.7	10.2	9.77	11.5	10.4	88
3	9.3	3.0	17.4	9.63	19.3	9.34	19	7.29	14.1	9.9	56
4	5.3	5.3	13.3	4.44	14.3	7	14.9	10.9	23.1	12.1	62
5	9.3	4.9	14	4.77	18.1	6.11	N.A.	N.A.	21.4	7.6	48
6	2.0	1.4	5.6	3.4	13.1	9.61	13.4	6.32	14.9	10.2	54
7	13.4	4.4	14.3	4.4	10.8	4.62	N.A.	N.A.	18	4.6	46
8	8.7	5.1	14.5	5.11	17.4	6.7	N.A.	N.A.	17.4	6.7	24
9	15.3	5.6	18.6	6.34	21.3	7.74	N.A.	N.A.	23.6	11.6	26

ACTH = adrenocorticotropic hormone, N.A. = not assessed.

Table 5

Summary of patients' course.

ACTH value before hydrocortisone replacement therapy (μg/dL)	ACTH value after hydrocortisone replacement therapy (μg/dL)	Cortisol value before hydrocortisone replacement therapy (μg/dL)	Cortisol value after hydrocortisone replacement therapy (μg/dL)	Observation period (mo)	Number of the patients who could stop hydrocortisone replacement therapy
8.5 ± 4.2 *P = .015	20.0 ± 6.8	4.5 ± 1.3 *P = .001	9.4 ± 2.5	51.6 ± 18.2	5 (55.6%)

Data are shown as mean ± standard deviation.

ACTH = adrenocorticotropic hormone.

*P < .05 was considered significant.

Table 6

The results of univariate regression analysis.

	Improvement of morning plasma ACTH value (pg/mL)	Improvement of morning serum cortisol value (μg/dL)
Age (yr)	P = .407 (95% CI: −0.32, 0.71)	P = .581 (95% CI: −0.17, 0.29)
Sex	P = .267 (95% CI: −18.53, 6.02)	P = .211 (95% CI: −8.02, 2.13)
Body mass index (kg/m^2)	P = .405 (95% CI: −1.64, 0.75)	P = .083 (95% CI: −0.79, 0.06)
Morning plasma ACTH value at diagnosis (pg/mL)	P = .594 (95% CI: −1.62, 0.99)	P = .504 (95% CI: −0.79, 0.22)
Morning serum cortisol value at diagnosis (μg/dL)	P = .221 (95% CI: −2.84, 5.24)	P = .286 (95% CI: −2.41, 0.83)

ACTH = adrenocorticotropic hormone, CI = confidence interval.

and serum cortisol value was not measured after hydrocortisone replacement therapy.[19]

Furthermore, we demonstrated that ihAI could recover with hydrocortisone replacement therapy. Commonly, patients with AI (e.g., isolated ACTH deficiency) cannot discontinue hydrocortisone replacement therapy.[2] Meanwhile, it was previously reported that hydrocortiosone replacement therapy could improve ACTH and corisol secretion of the patient with hypothalamic AI.[20] In the present study, plasma ACTH and serum cortisol values of all patients improved after the observation period, and 5 patients could discontinue hydrocortisone replacement therapy. The results in the present and previous studies indicated ihAI could be due to excess stress. Excess stress could cause the impoverishment of the hypothalamus and inadequate secretion of CRH. Therefore, hydrocortisone replacement therapy could help recover their "exhausted" CRH secretion of the hypothalamus. In comparison with this, regression analysis could not reveal a significant relationship between improvement in morning plasma ACTH or serum cortisol value and considerable parameters except body mass index, which was associated with improvement in morning serum cortisol value. Nevertheless, AI is known to cause weight loss. In order to confirm the relationship and reveal the reason, future studies with a large cohort are required. The present study was small and difficult to analyze because ihAI is quite rare.

We also demonstrated that patients with ihAI did not have hyponatremia, hyperkalemia, and eosinophilia, which were considered the typical symptoms of AI. The reason is unclear, but almost all of the patients with hypothalamic AI reported in a recent study also did not have hyponatremia, hyperkalemia, and eosinophilia.[19] Therefore, these could be a characteristic feature of ihAI. Thus, from the results of the present study, we recommend that clinicians and endocrinologists should consider the possibility of ihAI if patients have the symptoms possibly related to AI lacking hyponatremia, hyperkalemia, and eosinophilia. Our study has 2 limitations. The study cohort of this study was small because ihAI were rare. In addition, the recent study indicated the well-known cortisol cutoff values might be lower with current assays to diagnose AI.[21] Hence, future studies are also required to confirm these perspectives.

5. Conclusion

The present study is the first of our knowledge to demonstrate the clinical improvement of patients with ihAI by terms of hydrocortisone replacement therapy. This novel therapeutic option will promise drastic changes in the patients' quality of life and reduce the risk of adrenal crisis. We hope future studies will confirm the characteristics and further insights into the mechanism.

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