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## Twelve patients with mental illness who complained of postprandial symptoms in addition to fatigue showed central adrenal insufficiency

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### ABSTRACT

**Background:** Adrenal insufficiency (AI) may cause psychiatric symptoms. We evaluated the correlation between the hypothalamic-pituitary-adrenal axis (HPA) function in patients with mental illness who complained of postprandial symptoms in addition to fatigue.

**Methods:** We recruited 16 patients with mental illness who complained of postprandial symptoms in addition to fatigue for the evaluation of the HPA axis function using a rapid adrenocorticotropin (ACTH) test with Cortrosyn®, (250 µg), a corticotropin-releasing hormone (CRH) test, and an insulin tolerance test (ITT). The ITT results were adopted if the nadir blood glucose level was <2.2 mm/L. Patients with showed a peak cortisol level of <496.6 nmol/L (18 µg/dL) in the ITT were diagnosed with AI and the results were compared with the results of the rapid ACTH and CRH tests. The patients' clinical characteristics were evaluated.

**Results:** Twelve of 16 patients met the criteria for the adoption of the ITT. A peak cortisol level of <496.6 nmol/L was detected by the rapid ACTH test in three patients, by the CRH test in ten patients, and by the ITT in all twelve patients. Six of the above 12 patients used exogenous steroids due to the comorbidities such as bronchial asthma.

**Conclusions:** Twelve of the patients who complained of postprandial symptoms in addition to fatigue met the diagnostic criteria for AI. AI is often latent and more frequent in patients with mental illness. It is therefore necessary to inquire about exogenous steroid use for comorbidities when managing such patients.

### 1. Introduction

Individuals living with mental illness who experience depression and anorexia nervosa sometimes complain about postprandial symptoms [1]. In general, patients with depression and anorexia nervosa have a hyperactive hypothalamic-pituitary-adrenal (HPA) axis [2]. However, the symptoms of fatigue, dizziness, or nausea triggered by postprandial symptoms in patients with mental illnesses resemble those of adrenal insufficiency (AI) [3]. The link between AI and mental illness is not fully understood.

Rather than distinguishing between mental illness and AI, we hypothesized that AI might be concomitant in patients with depression, anorexia nervosa, and other conditions who complained of postprandial symptoms in addition to fatigue. We report the results of the HPA axis in

the above patients with mental illness and the comorbidities, history of past illness, history of exogenous steroid use, and psychological stress, and discuss the relationship between these factors and AI.

### 2. Materials and methods

#### 2.1. Case-series study

Patients attending the psychosomatic clinic in Fukuoka Tokushukai Hospital between January 1, 2017, and December 31, 2019, were asked about fatigue and unpleasant postprandial symptoms in the past month, and cases with fatigue and postprandial symptoms were tested for the HPA axis, considering the possibility of AI. During this period, 16 patients met the selection criteria and were considered AI suspects. During

**Abbreviations:** ACTH, adrenocorticotropin; AI, adrenal insufficiency; BDI, Beck depression inventory; BMI, body mass index; CRH, corticotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; ITT, insulin tolerance test.

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the study period, a total of 2808 new patients came to the above clinic. Since the questions were not structured, some selection bias was considered to exist, making this study a case-series study and not a case-control study.

## 2.2. HPA axis function tests and patients' clinical characteristics

According to the sensitivity of the diagnosis of AI [4], the rapid ACTH test, a corticotropin-releasing hormone (CRH) test, and an insulin tolerance test (ITT) were performed. The rapid ACTH test involved the intravenous administration of 250 µg of Cortrosyn® (synthetic ACTH 1–24, Dai-Ichi Sankyo), the CRH test involved the intravenous administration of 100 µg of CRH (CRH®, human Corticorelin, Mitsubishi Tanabe Pharma, Osaka, Japan), and the ITT involved the intravenous injection of 0.1 IU/kg body weight insulin (Novolin R®; Novo Nordisk A/R, Tokyo, Japan). All tests were carried out from 0830 to 0930 in a fasting state on different days. The ITT was considered successful when the nadir blood glucose was <2.2 mmol/L. Among the 16 patients, 12 had a nadir blood glucose level <2.2 mmol/L in response to ITT. The cortisol and ACTH levels in response to ITT in these 12 patients were therefore adopted. The peak cortisol levels in these 12 patients in response to the three different stimuli (ACTH, CRH, and ITT) were then compared. The clinical characteristics of these 12 patients were collected from the patients' electronic medical records.

The cortisol and ACTH testing kits were obtained from Roche Diagnostics (Tokyo, Japan). The reference ranges of the serum cortisol and plasma ACTH levels were 172.2–496.6 nmol/L and 1.6–13.9 pmol/L, respectively.

A peak serum cortisol of <496.6 nmol/L in response to stimuli was considered to indicate AI [3]. Among patients with AI, a peak ACTH to basal ACTH ratio of <2 in response to the CRH test was considered to indicate ACTH deficiency [3].

## 2.3. Hydrocortisone replacement therapy

The patients diagnosed with AI were given psychological education and supportive approaches to avoid physical and mental stress. When severe fatigue or postprandial symptoms that limited the social activity of AI patients occurred, 10–30 mg of hydrocortisone replacement therapy was suggested.

## 2.4. Statistical analyses

Data were expressed as the mean ± standard deviation or the actual number. An analysis of variance (ANOVA) was performed to determine the statistical significance of differences between variables. A chi-squared test was performed to examine the differences between the categorical variables and a paired *t*-test was performed to compare the mean differences between the two groups were used. The JMP 13.1 software program (SAS Institute, Tokyo, Japan) was used to perform the statistical analyses. *P* values of <0.05 were considered to indicate statistical significance.

## 2.5. Ethical considerations

All participants provided their written informed consent. The present study was performed in accordance with the Declaration of Helsinki as amended in 2008. The present study was approved by the Ethics Committee of Fukuoka Tokushukai Hospital (Approval No. 191101).

## 3. Results

### 3.1. Demographic and clinical characteristics

The median age of the 12 patients was 37 years old (range: 17–62 years). The study population included two men and ten women. Eight of

the 12 patients were diagnosed with depression. The mental illness of the remaining patients included somatic symptom disorder, panic disorder, myalgic encephalomyelitis/chronic fatigue syndrome, and anorexia nervosa. The median body mass index (BMI) was 19.7 (range: 13.4–28.1). The median duration of illness was five years (range: 2–8 years). The Beck depression inventory (BDI) was 25.5 ± 10.4; 11 patients had a high BDI of ≥16. The patients' postprandial symptoms included anxiety (*n* = 7), low-grade fever (*n* = 4), headache (*n* = 6), palpitations (*n* = 8), dizziness (*n* = 3), and nausea (*n* = 10). Ten of the 12 patients reported experiencing psychological stress at their workplace, home, or school, and 10 had comorbidities including autoimmune thyroid disease (*n* = 2), bronchial asthma (*n* = 3), allergic rhinitis (*n* = 1), allergic dermatitis (*n* = 2), and eating disorders (*n* = 5). One patient had a past early childhood history of nephrotic syndrome. Six of the 12 patients had used exogenous steroids, including inhaled steroids (*n* = 3), topical steroids (*n* = 2), nasal steroids (*n* = 1), and oral steroids (*n* = 1); patient number 11 used an inhaled steroid for bronchial asthma and oral steroids for nephrotic syndrome during childhood (Table 1). The details concerning the medicine, dose, and duration of exogenous steroids that were used are listed in Table 1. One of the 12 patients had hyponatremia and none of the 12 patients had hypereosinophilia. The basal serum cortisol level was 170.3 ± 80.0 nmol/L, and the plasma ACTH level was 2.9 ± 1.7 pmol/L. The serum cortisol levels in eight patients and the plasma ACTH levels in three patients were below the normal reference range.

### 3.2. The HPA axis

A rapid ACTH test showed a peak cortisol level <496.6 nmol/L in 3 patients, but the CRH test showed a peak cortisol level <496.6 nmol/L in 10 patients, and the ITT, which has been considered the gold standard for the evaluation of the HPA axis [5], showed a peak cortisol level of ~480.0 nmol/L in all the 12 patients (Fig. 1a).

In the CRH test, the ACTH peak/basal level ratio was 5.7 ± 2.6. On the other hand, in the ITT test, the ACTH peak/basal level ratio was 4.2 ± 3.4, and there were two patients with a value < 2. There were no significant differences in the ACTH peak/basal ratio between the CRH test and the ITT (*t* = -1.24827, *p* = 0.2378) (Fig. 1b).

### 3.3. The effect of hydrocortisone replacement therapy on social activity and clinical symptoms

Nine patients who requested replacement therapy for AI were given 10 mg of hydrocortisone initially. The dose of hydrocortisone was increased according to the clinical symptoms up to 30 mg. Seven of the nine patients were able to return to their workplace or school. The remaining two were unable to return to their workplace or school, but their symptoms improved, and there was no change in the social activity of the three patients who did not request hydrocortisone replacement therapy.

## 4. Discussion

We found AI in the patients in the present study, which was contrary to the activation of the HPA axis according to the diagnostic criteria of the ITT. The ITT is the gold standard test for AI [5] and enabled the enrollment of patients who met the diagnostic criteria for AI. However, according to the rapid ACTH test, only 3 of the 12 patients achieved a peak cortisol level of <496.6 nmol/L. Using the CRH test, 10 of the 12 enrolled patients had a peak cortisol level of <496.6 nmol/L, which was almost the same result as the ITT test [6]. It showed that, in comparison to the rapid ACTH test, the CRH test provided a more accurate assessment of the HPA axis function in patients with bronchial asthma.

The basal ACTH levels of the studied patients were lower than the reference range or at the low end of the reference range. Thus, the cause of AI was considered to be central rather than primary [3]. Moreover, an

**Table 1**  
Demographics, clinical characteristics, and laboratory findings of patients with mental illness who complained of postprandial symptoms in addition to fatigue.

case	1	2	3	4	5	6	7	8	9	10	11	12
age (years)	62	44	34	27	17	47	36	42	41	22	38	32
Sex	F	M	F	F	M	F	F	F	F	F	F	F
mental illness*	D	D	D	PD	SSD	D	D	ME/CFS	D	D	D	AN
duration of illness (years)	3	6	7	7	2	3	2	8	3	7	6	4
BMI*	24.7	28.1	20.9	17.1	22.9	23.0	15.8	27.2	18.5	16.7	13.4	16.8
BDI*	22	14	20	20	22	18	43	28	16	45	36	22
postprandial symptoms												
anxiety	yes	Yes	yes	yes	No	no	no	no	yes	yes	yes	no
low grade fever	no	No	yes	no	Yes	no	no	yes	yes	no	no	no
headache	no	Yes	yes	yes	Yes	no	no	yes	no	yes	no	no
palpitation	yes	No	yes	yes	No	yes	yes	yes	yes	yes	no	no
dizziness	yes	No	yes	no	No	no	no	no	yes	yes	no	no
nausea	yes	No	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
psychological stress												
home			yes		yes			yes	yes			yes
work place	yes	Yes				yes	yes					
school										yes		
comorbidity*	AITD AR	BA	AITD AN	AN	AD		AN		BA	OSFSD	BA OSFED	AD
previous history*											NS	
steroid user	yes nasal	yes inhale-d			yes topical				yes inhale-d		yes inhale-d orally in childho-od)	yes topical
steroids administered*	Mom	Bud			Beta				Flu		1 Flu 2 PRL	Beta
dose of steroids	200 µg/day	320 µg/day			0.12%				200 µg/day		1400 µg/day 2 10–30 mg/ day	0.12%
duration of steroids used (years)	>5	>10			>6				>5		1 > 5 ②0.25	4–5
laboratory findings												
serum Na (mmol/L)	141	144	140	139	141	141	139	140	141	139	141	130
peripheral eosinophil (%)	2	3	4	3	3	2	1	5	4	5	2	4
basal serum cortisol level (µmol/L)	168.3	151.7	171.1	389.0	190.4	140.7	96.4	126.9	113.1	231.7	140.7	242.8
basal plasma ACTH level (pmol/L)	3.0	1.0	2.8	6.8	2.7	4.2	1.2	4.0	2.7	4.2	0.7	1.7
peak cortisol to rapid ACTH level (µmol/L)	458.0	480.0	675.9	629.0	518.7	507.6	606.9	524.2	441.4	505.9	658.6	570.6
peak cortisol level to CRH test (µmol/L)	361.4	386.2	513.1	480.0	424.9	369.0	408.3	424.7	353.1	469.0	413.8	489.3
peak ACTH level to CRH test (pmol/L)	15.0	6.6	13.7	15.0	16.7	10.1	8.3	20.8	16.7	13.0	4.8	20.6
peak cortisol level to ITT (mmol/L)	369.7	427.6	463.5	491.1	366.9	220.7	311.7	383.5	295.2	386.2	474.5	438.7
peak ACTH level to IIT (pmol/L)	21.6	5.2	6.7	35.4	3.2	6.7	2.6	17.2	7.3	8.4	9.3	4.8
hydrocortisone* (HC) replacement therapy												
dose of HC (mg/day)	15	10	10	no	15	15	15	25	30	30	no	no
the effect of HC replacement therapy on social activity or symptoms	return to workp-lace	improvement of sympt-oms	return to workp-lace	not remar-kable change	return to school	improvement of sympt-oms	return to workp-lace	return to workp-lace	return to workp-lace	return to school	not remar-kable change	not remar-kable change

Mean ± SD; age, 37 ± 12 years; duration of illness, 3 ± 2 years; BMI, 20.4 ± 4.8 kg/m<sup>2</sup>; BDI, 26 ± 10; serum Na, 140 ± 4 mmol/L; peripheral eosinophil, 3 ± 1 (%); basal serum cortisol, 170.32 ± 80.01 nmol/L; basal plasma ACTH, 2.90 ± 1.74 pmol/L; basal plasma adrenaline, 68.24 ± 32.21 pmol/L; basal plasma noradrenaline, 626.57 ± 404.90 pmol/L.

\*Abbreviations; AD, allergic dermatitis; AITD, autoimmune thyroid disease; AN, anorexia nervosa; AR, allergic rhinitis; BA, bronchial asthma; BDI, Beck depression inventory; Bet, betamethasone valerate; BMI, body mass index; Bud, budesonide; D, depression; Flu, fluticasone; HC, hydrocortisone; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; Mom, mometasone; NS, nephrotic syndrome; OSFED, other specified feeding or eating disorders; PD panic disorder; PSL, prednisolone; SSD, somatic symptom disorder.

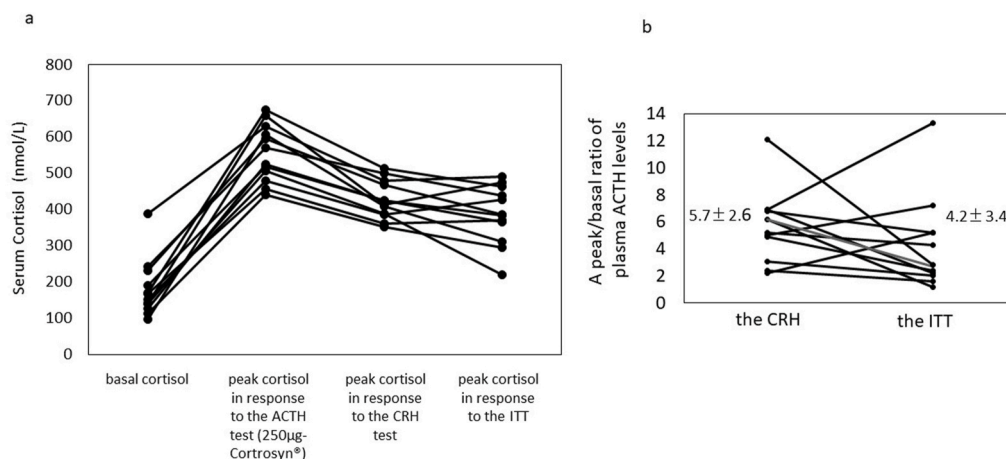


Fig. 1. Basal and peak cortisol levels in response to three stimuli of the rapid ACTH test, the CRH test and the insulin tolerance test (ITT) (a) and a peak/basal ratio of plasma ACTH to the CRH test and to the ITT (b) in patients with mental illness who complained of postprandial symptoms in addition to fatigue.

ACTH peak/basal ratio of  $>2$  in the CRH test except for a few patients in this study means that the cause of AI could be considered to be an aberrant hypothalamus function rather than the pituitary function [3].

The patients in our study were eligible for a diagnosis of hypothalamic AI. However, the patients did not show hyponatremia (with the exception of 1 patient), hypereosinophilia, or require an emergency room visit, despite their postprandial symptoms. It is likely that their condition was comorbid with a long-standing mild or latent AI.

The majority of patients with mental illness concomitant with AI in this study who received hydrocortisone replacement therapy were able to return to their workplace or school. The clinical symptoms of these patients with mental illness concomitant with AI may therefore be somewhat involved with AI.

The precise cause of the AI in these patients with mental illness is unclear. One possible explanation is the use of exogenous steroids such as inhaled steroids, nasal steroids, or topical steroids, for past or present comorbidities [7]. Six of the studied patients were steroid users. Almost 20% of patients with bronchial asthma who use inhaled steroids have AI [8]. It is necessary to inquire about exogenous steroid use due to comorbidities in patients with mental illness. However, six of the patients did not use exogenous steroids. There were no clear cause for AI in these patients other than their history of exogenous steroids. In animal study, it was reported that chronic psychological stress can produce allostatic load and contribute to a decreased cortisol response [9]. However, it is not confirmed in human. Psychological stress as well as physical stresses such as infection and trauma might provoke the onset of AI [10].

The prevalence of primary AI and secondary AI is estimated to be 82–144/million and 150–280/million, respectively [11]. We found at least 12 patients with AI among 2808 patients with mental illness during the study period, which would equivalent to a prevalence of  $>4000$ /million.

## 5. Conclusion

Patients with mental illness who complain of postprandial symptoms in addition to fatigue met the criteria for AI. The present study suggested that central, especially hypothalamic AIs are latent and more frequent in patients with mental illness. It is necessary to inquire about exogenous steroid use when managing patients with mental illness.

### 5.1. Limitations

The present findings of the HPA axis in patients with mental illness such as depression and anorexia nervosa, and other conditions who

complained of postprandial symptoms in addition to fatigue, were obtained at a single center. Furthermore, the results of the HPA axis were obtained from a small number of patients.

## Author contributions

Sunao Matsubayashi: The physician of the enrolled patients, Contributed to the HPA axis tests, Collection of electronic medical records and Writing original draft paper. Shuichi Matsumoto: Physician of the enrolled patients and Critical revision of the draft of the paper. Yuhki Senda: Physician of the enrolled patients and Contributed to the HPA axis tests Nobuhiro Nakatake: Physician of the enrolled patients, Contributed to the HPA axis tests and Critical revision of the draft paper Takeshi Hara: Physician of the enrolled patients and Critical revision of the draft paper. All authors approved the final version of the paper for submission.

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## Declaration of conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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