<Original Article>

Characteristics of Patients Diagnosed with Adrenal Insufficiency in the General Medicine Department of a University Hospital: A Single-Center Descriptive Study

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ABSTRACT

Background: Adrenal insufficiency (AI) presents with several nonspecific symptoms that can lead to delayed diagnosis, misdiagnosis, and decreased quality of life. This study aimed to identify the clinical profiles of patients with AI who consulted to a university hospital general medicine department.

Methods: Cross-sectional data were retrospectively extracted from the medical records of patients with suspected AI who visited the general medicine department at university hospitals in Japan between October 2015 and March 2019 and who underwent stimulation tests. Age–sex adjusted logistic regression analysis was performed with various clinical signs as explanatory variables and AI diagnosis as the objective variable.

Results: Of the 122 study subjects, 82 (67.2 %) were women, 24 of whom were diagnosed as AI. Age–sex adjusted logistic regression analysis revealed that the odds ratio (OR) per unit increase in random blood cortisol (OR: 0.74, (95 % confidence interval [CI] 0.60–0.92)) was associated with a diagnosis of AI. However, the OR per unit increase in random blood adrenocorticotropic hormone (OR: 0.97, 95 % CI 0.93–1.03) was not. General fatigue (OR 5.5, 95 % CI 0.65–46.2), weight loss (OR 2.47, 95 % CI 0.78–7.82), and hypotension (OR 11.5, 95 % CI 1.05–125.6) were also associated with AI diagnosis.

Conclusions: Clinical signs such as general fatigue, weight loss and hypotension were significant predictors of AI. The results suggest that several patients who visit the general medicine department at university hospitals in Japan have conditions that are difficult to diagnose based on the test results. Prospective studies in general medicine departments of several hospitals are required to validate the generalizability of these results.

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INTRODUCTION

Adrenal insufficiency (AI) is caused by a relative or absolute deficiency of steroid hormones secreted by the adrenal glands. It can be divided into primary adrenal insufficiency (PAI), secondary adrenal insufficiency (SAI) and tertiary adrenal insufficiency (TAI), depending on whether the disease process affects the adrenal cortex, anterior pituitary gland or the hypothalamus, respectively [1]. TAI is often subsumed under SAI [2, 3]. An epidemiological Japanese study found that PAI affected 911 patients in 5 years [3, 4].

The prevalence of PAI and AI [4, 5] are increasing with physicians' awareness of these disorders [6, 7]. SAI has been reported more frequently than PAI, with a prevalence of up to 42 cases per 100,000 population based on European studies [6].

Clinical symptoms and signs of AI are associated with hormone deficiencies and often appear gradually over an extended period. The main symptoms associated with cortisol deficiency include general fatigue, hypotension, and weight loss; however, these symptoms are nonspecific and often lead to delayed diagnosis and misdiagnosis [1]. Approximately half of all patients with SAI exhibit symptoms that persist for more than a year, the majority of whom have had to consult three or more physicians before obtaining a diagnosis [8, 9]. TAI also often goes undiagnosed and is managed by nonspecialized departments [10]. Patients with a delayed diagnosis of AI have a significantly worse quality of life than patients without a delayed diagnosis [8]. A timely diagnosis of AI is critical to prevent long-term adverse effects and adrenal crisis. When basal serum cortisol level is in the range < 4 μg/dL, or ≥ 4 μg/dL but < 18 μg/dL (approximately 500 nmol/L), an ACTH stimulation test (synthetic 1-24 ACTH: CORTROSYN 250 μg iv) is highly recommended [11].

Diagnosing AI often takes a prolonged time, delaying appropriate referral to a specialist; however, the actual extent of this issue remains unknown. The majority of reports on clinical signs and physical and laboratory findings, among others, of AI are from specialty departments, with only a few reports from general medicine departments [12]. In particular, the general medicine departments of university hospitals in Japan tend to accumulate highly complex or difficult-to-diagnose cases [13].

This study analyzed the clinical profiles of patients with suspected AI using patient data collected from the general medicine department of a university hospital to contribute data for future diagnostic tools.

MATERIALS AND METHODS

Study design

Cross-sectional study

Participants

Participants were selected from patients who visited the department of general medicine in a university hospital between October 1, 2015 and March 31, 2019. The total number of patients was 8,045, among whom 4,990 (62.0 %) were female. The average age was 49.6 years, and 3,272 patients (40.7 %) were referred from other hospitals.

The study included 122 patients with suspected AI who were admitted to the general medicine department and underwent ACTH stimulation test. Their basal serum or randam cortisol level is less than 18 μg/dL (approximately 500 nmol/L) and the attending physician has determined that ACTH stimulation test is necessary. No patient was receiving glucocorticoids exceeding the physiological dose at the time of the stimulation test.

Data

Patient IDs were mechanically extracted for patients who visited the general medicine department between January 1, 2015, and December 31, 2019, and met the following receipt computerization codes:

D287-00 ACTH stimulation test (Mineralocorticoid) 16 0120210

D287-00 ACTH stimulation test (Glucocorticoid) 16012 0310

D287-00 Anterior pituitary stimulation test (ACTH) 16 0120110

The dates these data were accessed for research purposes were from August 11 to September 21, 2023. A total of 123 patients were included in the analysis. The authors reviewed electronic medical records and found that only 122 patients actually underwent a stimulation test, and 1 was excluded. In total, 122 patients' background data were extracted, including age, sex, clinical symptoms, abnormal laboratory values, and stimulation tests results. For ordinal data such as clinical signs, cases that were not clearly documented in the medical records were assumed to have no signs, and such instances were not considered as missing information.

In the 11 patients who did not undergo ACTH measurement at the time of the outpatient visit, data from the ACTH stimulation test were used. Missing laboratory (quantitative) data (10 cortisol and 1 ACTH random) were excluded from the analysis.

Variables

Objective variables

The objective variable was a diagnosis of AI. In Japan, when early morning cortisol is less than 18 μg/dL, an ACTH stimulation test (synthetic 1-24 ACTH: CORTROSYN 250 μg iv) is performed because AI cannot be ruled out [11]. Patients with a peak blood cortisol level < 18 μg/dL during the ACTH stimulation test, requiring cortisol replacement, were diagnosed with AI.

Explanatory variables

The following were analyzed as explanatory variables: age; sex; ambulatory random cortisol levels; random ACTH levels; general fatigue and weight loss; headache; gastrointestinal symptoms (e.g., nausea, vomiting, constipation, abdominal pain); musculoskeletal symptoms (e.g., muscle pain, joint pain); mental symptoms (e.g., decreased libido, disorientation, anxiety, personality changes); hypotension (systolic blood pressure < 90 mmHg); skin symptoms (e.g., pigmentation, loss of axillary/pubic hair); hyponatremia (sodium < 138 mEq/L); hyperkalemia (potassium > 4.8 mEq/L); hypoglycemia (blood glucose < 73 mg/dL); anemia (hemoglobin < 13.7 mg/dL in men and < 11.6 mg/dL in women), and hypereosinophilia (eosinophils > 500/μL).

Clinical signs and laboratory findings were selected based on previous reports [6]. The presence or absence of clinical symptoms was determined based on whether they were documented in the electronic medical record. Reference values for laboratory findings were determined according to the standards of our hospital.

Statistical analysis

Patient background information was described separately for patients with and without AI (**Table 1**). Because a normal distribution could not be assumed for continuous variables, they were expressed as median and interquartile range. Comparisons between patients with and without AI were made using the Wilcoxon rank sum test and *P* values were calculated. For nominal variables, the proportion of each category was calculated, and a chi-square test was performed to calculate the *P* value. To remove the influence of sex and age, we analyzed the clinical signs and laboratory findings associated with AI using sex- and age-adjusted logistic regression analysis (**Table 2**) and calculated 95 % confidence intervals (CI). Due to sex bias, we have added a sensitivity analysis stratified by sex (Supplementary **Table 1**). A *P* value of 0.05 was considered to indicate a significant difference. Statistical analysis was performed using JMP Pro 15.0 (SAS, Cary, NC, USA).

Ethical consideration

This study was conducted in compliance with applicable norms and guidelines, including the Declaration of Helsinki of the World Medical Association and the Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects. Information about the study was notified to the public through the website of the Department of General Medicine was placed in a location where research subjects and others could easily learn about the study (opt-out option was provided). Data were handled as patient IDs rather than individual names. This study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (approval number: 2022-183) on 15/02/2023.

RESULTS

Of the 122 patients, 82 (67.2 %) were female. The median age was 43, and there was no significant difference across the sex. One patient had the highest cortisol level of less than 18 μg/dL in the ACTH stimulation test, but this did not lead to a diagnosis of AI. In total, 24 (19.7 %) patients, 11 males and 13 females, were included in the AI group. AI prevalence was approximately 1.7 times higher in men than in women (**Table 1**).

Median cortisol levels were 5.82 μg/dL overall, 4.42 μg/dL in the group with AI, and 5.97 μg/dL in the group without AI. Significantly lower cortisol levels were observed in the AI group. Median ACTH levels were 12.8 pg/mL overall, 13.5 pg/mL in the AI group, and 16.3 pg/mL in the without AI group, with no significant differences. No cases in the AI group exceeded baseline ACTH levels (**Table 1**).

Table 2 shows the results of age-sex adjusted logistic regression analyses. The odds ratio (OR) per unit rise in random cortisol levels was 0.74 (95 % CI 0.60–0.92), which was associated with a diagnosis of AI. The OR per unit increase in random ACTH levels was 0.97 (95 % CI 0.93–1.03). General fatigue (OR 5.10, 95 % CI 1.35–19.5), weight loss (OR 2.97, 95 % CI 1.05–8.37), and hypotension (OR 9.63, 95 % CI 1.42–65.1) were associated with AI diagnosis. Musculoskeletal and skin symptoms also tended to be associated with AI diagnosis. Hyponatremia, hypoglycemia, anemia, and eosinophilia had large 95 % CIs but were not clearly associated with AI diagnosis. Hypokalemia could not be analyzed because of insufficient data.

Logistic regression analysis stratified by sex and adjusted for age revealed no sex-related differences in general fatigue, weight loss, musculoskeletal symptoms, psychiatric symptoms, and eosinophilia. However, sex-related differences in headache incidence, digestive symptoms, hyponatremia, and anemia were observed (Supplementary **Table 1**).

DISCUSSION

Summary of the results

Multivariate logistic regression analysis adjusted for age and sex showed that general fatigue (OR 5.1, 95 % CI 1.35–19.5), weight loss (OR 2.97, 95 % CI 1.05–8.37), and hypotension (OR 9.63, 95 % CI 1.42–65.1) were associated with AI diagnosis. However, laboratory findings showed no clinically significant differences except for cortisol levels.

Findings in context

A morning serum cortisol of < 140 nmol/l (5 μg/dl) in combination with increased ACTH levels (twice the upper normal limit) is confirmative of PAI [6]. Diagnostic tools for SAI vary widely between countries and even between endocrine centers in the same country, and no generally

Table 1 Descriptive statistics on the presence of adrenal insufficiency by patient background

	Whole n = 122	Adrenal insufficiency n = 24 (19.7 %)	No adrenal insufficiency n = 98 (80.3 %)
Age, years (median, IQR)	43 (28.75–51)	44 (34.5–52.25)	43 (26.75–51)
Sex			
Male	40	11	29
Female	82	13	69
Serum cortisol (μg/dL) (median, IQR)	5.82 (4.39–8.36)	4.42 (2.1–5.93)	5.97 (4.45–8.81)
ACTH (pg/mL) (median, IQR)	12.75 (9.05–19.73)	12.4 (8.9–18.6)	12.8 (9.1–19.8)
General fatigue			
Exist	82	21	61
None	40	3	37
Weight loss			
Exist	23	8	15
None	99	16	83
Headache			
Exist	27	5	22
None	95	19	76
Gastrointestinal symptoms			
Exist	38	9	29
None	84	15	69
Musculoskeletal symptoms			
Exist	38	12	27
None	84	12	71
Psychiatric symptoms			
Exist	51	12	39
None	71	12	59
Hypotension			
Exist	5	3	2
None	117	21	96
Skin symptoms			
Exist	4	2	2
None	118	22	96
Hyponatremia			
Exist	7	2	5
None	115	22	93
Hyperkalemia			
Exist	1	0	1
None	121	24	97
Hypoglycemia			
Exist	2	1	1
None	120	23	97
Anemia			
None	105	18	87
Exist	17	6	11
Eosinophilia			
Exist	8	3	5
None	114	21	93

IQR, interquartile range; ACTH, adrenocorticotropic hormone

Table 2 AI using sex- and age-adjusted logistic regression analysis

	Univariate analysis			Multivariate analysis		
	Crude odds ratio	95 % Confidence interval [95 % CI]	*P*-value	Adjusted odds ratio (age, sex)	95 % Confidence interval [95 % CI]	*P*-value
Age (by 10 years)	1.17	[0.91–1.50]	0.22			
Sex (Ref: male)	0.50	[0.20–1.24]	0.13			
Cortisol level (per 1 μg/dL)	0.76	[0.61–0.93]	0.00	0.74	[0.60–0.92]	0.007
ACTH (per 1 pg/mL)	0.98	[0.94–1.03]	0.49	0.97	[0.93–1.02]	0.33
General fatigue	4.25	[1.18–15.22]	0.03	5.12	[1.35–19.50]	0.017
Weight loss	2.77	[1.01–7.61]	0.05	2.97	[1.05–8.37]	0.04
Headache	0.91	[0.30–2.71]	0.86	0.91	[0.30–2.78]	0.87
Gastrointestinal symptoms	1.43	[0.56–3.63]	0.45	1.59	[0.61–4.15]	0.35
Musculoskeletal symptoms	2.63	[1.05–6.56]	0.04	2.46	[0.97–6.24]	0.06
Psychiatric symptoms	1.51	[0.62–3.71]	0.37	1.73	[0.68–4.36]	0.25
Hypotension	6.86	[1.08–43.62]	0.04	9.63	[1.42–65.10]	0.02
Skin symptoms	4.36	[0.58–32.70]	0.15	5.81	[0.74–45.60]	0.09
Hyponatremia	1.69	[0.31–9.30]	0.55	1.12	[0.18–6.94]	0.90
Hyperkalemia	N/A	N/A	N/A	N/A	N/A	N/A
Hypoglycemia	4.22	[0.25–69.97]	0.32	5.73	[0.33–99.0]	0.23
Anemia	2.64	[0.86–8.05]	0.09	2.3	[0.72–7.36]	0.16
Eosinophilia	2.66	[0.59–12.00]	0.20	2.07	[0.44–9.83]	0.36

ACTH, adrenocorticotropic hormone

established gold standard exists.

Although the risk of SAI was previously believed to be higher in women, a recent study showed that SAI was more common in men, with 194.5 cases per million women versus 248.4 cases per million men [14], consistent with the results of the present study [14].

With respect to symptoms and laboratory findings of AI, PAI differs from the typical features of SAI and TAI because it is deficient in both glucocorticoids and mineralocorticoids [15, 16]. SAI is usually milder than PAI because mineralocorticoid production is not impaired and AI is partial [17]. General fatigue, weight loss, and myalgia are primarily due to glucocorticoid deficiency, whereas hyponatremia and orthostatic hypotension are primarily due to mineralocorticoid deficiency [18]. SAI/TAI is less prominent in orthostatic hypotension and gastrointestinal symptoms because mineralocorticoid secretion is preserved [10]. This study showed that hypotension is associated with a diagnosis of AI, but it is less frequently associated with SAI than PAI because mineralocorticoid activity is not impaired in SAI [19]. However, this finding contradicts the hypothesis that SAI/TAI is responsible for most cases of AI. This may be because of differences in the age and ethnicity of the study subjects, blood pressure measurement methods, and definitions of hypotension.

The most common symptoms of SAI are general fatigue and decreased energy, followed by decreased libido, headache, axillary and pubic hair loss, dry and pale skin, and weight loss [20]. This is consistent with the findings of the present study, in which general fatigue was the most common symptom observed in the patients. The low incidence of symptoms such as decreased energy, decreased libido, and axillary and pubic hair loss may be due to the psychological difficulty of interviewing the patients or to the fact that patients were less likely to report these symptoms. The reason why statistically significant findings disappeared due to sex differences is that the number of cases was insufficient and the symptoms that patients emphasize and complain about may differ depending on sex (Supplementary **Table 1**).

Hyperkalemia caused by aldosterone deficiency has not been observed in patients with SAI but has been reported in 40 % of patients with PAI [21]. However, in the present study, hyperkalemia was observed in only one of 24 AI patients. Conversely, hyponatremia can occur in both PAI and SAI [1]. In SAI, cortisol deficiency leads to decreased free water excretion, causing dilutional hyponatremia similar to that observed in the syndrome of inappropriate antid-

iuretic hormone secretion [22]. In one study, 207 [84 %] of 247 patients with undiagnosed AI presented with hyponatremia. Unexplained hyponatremia should always be considered as AI [17]. Hyponatremia was not associated with a diagnosis of AI in the present study. In university general medicine departments, patients with general fatigue and weight loss, often linked to glucocorticoid deficiency or AI. These symptoms can occur even when characteristic laboratory abnormalities, such as hyponatremia and eosinophilia, are absent. This suggests that clinical symptoms alone may sometimes warrant further investigation for hormonal disorders.

Cortisol secretion is subject to diurnal fluctuations [17]. Early morning cortisol levels should be measured if SAI is suspected [2]. In the present study, random cortisol levels of the day were significantly lower in the AI group. However, the evaluation of random cortisol levels of the day has not been described in the literature. Thus, its utility as a substitute for early morning cortisol in the diagnosis of AI needs to be examined.

Clinical signs and laboratory findings with sex differences on logistic regression analysis stratified by sex and adjusted for age were difficult to evaluate because of the small study population.

Besides the fact that SAI/TAI is more common than PAI, other possible reasons why SAI/TAI accounted for the majority of patients with AI in this study may be owing to different patient characteristics and patient populations. According to a national survey of university general practice-related departments by the Japanese Association for Primary Care Alliance [23], university hospitals mainly treat difficult-to-diagnose and difficult-to-solve cases in outpatient and inpatient settings to meet social expectations. Patients with abnormal laboratory findings, such as hyponatremia, hyperkalemia, and eosinophilia, are more likely to be referred to specialized departments, whereas patients with nonspecific symptoms that are difficult to diagnose may be more likely to be referred to the general medicine departments of university hospitals.

Strengths and limitations

The main advantage of this study is that it was conducted in the setting of a university hospital general practice department that often encounter difficult-to-diagnose cases. This study may present evidence that patients who require treatment for AI do not receive treatment. Improving the accuracy of diagnosis of AI in general medicine departments may help to promptly and accurately refer patients to specialist departments.

However, this study has several limitations. First, this is a single-center, single-specialty study. The sample size was small, and patients in specialized departments were not included, thereby limiting the generalizability of the results. Thus, the results should be verified by collecting, analyzing, and comparing data using the same methods at other medical institutions involved in general practice, such as university and general hospitals. Second, because the study was conducted retrospectively, and data were extracted from electronic medical records, missing or misclassified data may be possible. Furthermore, the diagnosis of AI may involve other unmeasured factors. Because the most common cause of TAI is exogenous glucocorticoid use, a history of steroid-containing topical or inhalant medications and steroid-containing joint injections is particularly important and should be obtained [2]. Prospective studies in general medicine departments of several hospitals are required to validate the generalizability of these results.

Third, cases in which no endocrine stress test was performed were not studied, which may have created a possible selection bias. Future prospective studies should involve decision-making on conducting endocrine stress tests according to a precise protocol in principle.

CONCLUSIONS

In patients with suspected AI in the settings of general medicine at a university hospital, clinical signs such as general fatigue, weight loss, and hypotension were associated with AI. Low random cortisol levels were also useful in diagnosing AI. Prospective studies in several general medicine departments of university hospital are required to validate the generalizability of these results.

SUPPORTING INFORMATION CAPTION

S1 Table. Factors associated with adrenal insufficiency, stratified by sex

DATA AVAILABILITY STATEMENT

The data used in this study were collected from the patients of Osaka Medical and Pharmaceutical University Hospital which are not publicly available. The data are available from the authors upon reasonable request, with the permission from Osaka Medical and Pharmaceutical University Hospital. Please contact the corresponding author for this request.

FUNDING STATEMENT

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CONFLICT OF INTEREST DISCLOSURE

All authors state that there are no competing interests associated with this manuscript.

ETHICS APPROVAL STATEMENT

This study was conducted in compliance with applicable norms and guidelines including the Declaration of Helsinki of the World Medical Association and the Japanese Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects. This study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (approval number: 2022-183) on 15/02/2023.

PATIENT CONSENT STATEMENT

Owing to the nature of the retrospective cohort study using patients' medical records, patients' consent was not obtained in this study. Information about this study was notified to the public through the website of the Department of General Medicine (https://ompu.bvits.com/rinri/publish.aspx) and was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (approval number: 2022-183) on 15/02/2023. Also, the need of the informed consent was waived by Ethics Committee of Osaka Medical and Pharmaceutical University (approval number: 2022-183).

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

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