Possible adrenal insufficiency among fatigue patients in a psychosomatic medical clinic

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Abstract. Fatigue is a common symptom in patients visiting the clinic of psychosomatic medicine. A 250-μg synthetic ACTH (1–24) test (rapid ACTH test) and Beck depression inventory (BDI) were performed for 62 patients presenting with fatigue who visited the Department of Psychosomatic Medicine at Fukuoka Tokushukai Hospital. Patients were divided into 3 groups according to the serum cortisol response to the rapid ACTH test; those with a peak serum cortisol level of <15 μg/dL were defined as the adrenal insufficiency (AI) probable group, ≥15 μg/dL and <18 μg/dL as the AI suspected group, and ≥18 μg/dL as the non-AI group. Patients prescribed anti-depressants, had a BDI ≥16, and/or met the full criteria for major depression were diagnosed with depression. Five (8.0%) and 7 patients (11.3%) were assigned to the AI probable and AI suspected groups, respectively. All others were assigned to the non-AI group. Depression was observed in 37 patients (59.6%; 4 in the AI probable group [80.0%), 4 in the AI suspected group [57.1%), and 29 in the non-AI group [58.0%]). Users of exogenous steroids, such as inhaled steroids for bronchial asthma, were seen in the AI probable group (2; 40.0%), the AI suspected group (3; 42.8%), and the non-AI group (7; 14.0%) (χ² = 4.761, p = 0.0925). In conclusion, probable or suspected AI was observed in about one-fifth of patients presenting with fatigue at the psychosomatic medical clinic. A CRH test and insulin tolerance test (ITT) may help the mechanism underlying these possible AIs.

Key words: Fatigue, Depression, Psychosomatic medicine, Adrenal insufficiency, Exogenous steroids

FATIGUE is relatively common, with a prevalence of 6.0% to 25.0% according to population studies [1-4]. However, unexplained fatigue is not in frequent in a normal community setting. Fatigue is a feature of many common illnesses, with psychological, physiological, and physical causes. To diagnose the reasons for fatigue, a doctor will ask questions and take a sleep history and may perform a physical examination and blood tests. Patients with unexplained fatigue often visit the Clinic of Psychosomatic Medicine as outpatients in Japan, where many are diagnosed with depression [5, 6].

The presenting signs and symptoms of adrenal insufficiency (AI) are often non-specific, which often results in a delayed diagnosis of AI. The diagnosis of AI helps prevent adrenal crisis, which is a life-threatening disease [7]. Signs and symptoms of AI include fatigue (84%–95% of patients), a loss of appetite (53%–67%), weight loss (66%–76%), nausea and vomiting (49%–62%), and muscle and joint pain (36%–40%) [8].

It is valuable to evaluate the presence depression and AI in patients presenting with fatigue for over two weeks visiting the Clinic of Psychosomatic Medicine as outpatients.

Methods

Among patients who had complained of fatigue for over two weeks who visited the Department of Psychosomatic Medicine, Fukuoka Tokushukai Hospital, a central hospital supporting the community, from January 1, 2016, to December 31, 2017, in order to rule out AI according to the guideline of the Japan Endocrine Society [9], the cortisol levels at 9 am were evaluated in 64 patients (19 men and 45 women).

At the time of visiting the above department from other medical clinics, including our hospital, the patients with complaints of fatigue were usually ruled out from having active physical diseases. In our department, patients who complained of fatigue had a solid medical history, and additional tests were performed as needed, confirming again that they did not have any obvious physical illness. In other words, the patients’ conditions were well controlled, even if they had co-morbidities.

During the study period, patients newly visiting of the above department numbered 1,997. This study was a
A cross-sectional observational study. According to the guideline of the Japan Endocrine Society [9], cortisol levels <18 μg/dL were found in 62 patients (19 men and 43 women); this included levels <4 μg/dL in 5 patients and 4 to <18 μg/dL in the remaining 57 patients. These 62 patients were suspected of having AI, so, we performed a 250-μg synthetic ACTH [1–24] test (rapid ACTH test).

**Measurements**

Patients’ medical records, including their illness history and prescriptions, were checked using their electronic medical records. Physical diseases as comorbidities were well-controlled during the study.

A rapid ACTH test (CORTROSYN 250 μg intravenously; Daiichi-Sankyo Pharmaceutical Co, Tokyo, Japan) was performed from 8:30 to 9:00 in the morning. Based on the peak cortisol levels at 30 or 60 min after the rapid ACTH test, patients were divided into 3 groups; those with a peak serum cortisol level of <15 μg/dL were defined as the AI probable group, ≥15 to <18 μg/dL as the AI suspected group, and ≥18 μg/dL as the non-AI group [9]. The serum cortisol levels before and at 30 and 60 min after the test and the plasma ACTH before the test were assayed using kits from Roche Diagnostics (Tokyo, Japan). The reference ranges of serum cortisol and plasma ACTH were 6.24–18.0 μg/dL and 7.2–63.3 pg/mL, respectively. The background characteristics of these three groups were compared.

A Beck depression inventory (BDI) was performed. Patients with a history of on-going prescription of antidepressants, a BDI ≥16 or who met the full criteria of depression using the DSM-5 [10] were diagnosed as having depression.

**Statistical analyses**

Data are shown as the mean ± standard error (SE) or the actual number. The JMP 13.1 software program (SAS Institute, Tokyo, Japan) was used for performing the analysis of variance (ANOVA), and χ² tests were used for assessing differences between the AI and non-AI groups.

**Ethics**

This study was approved by the ethics committee of Fukuoka Tokushukai Hospital, Approval No. 300204.

**Results**

According to the response of serum cortisol to the rapid ACTH test (250-μg synthetic ACTH (1–24)), 5 (8.0%) and 7 (11.3%) patients were assigned to the AI probable and AI suspected groups, respectively. All others were assigned to the non-AI group (Fig. 1). The clinical characteristics of the above three groups were compared, and are shown in Table 1.

The age, sex, BMI, performance status (PS) [11], BDI, depression, and past history of psychological trauma were not markedly different among these three groups. Depression was seen frequently (59.6 %) in all participants (4 in the AI probable group [80.0%], 4 in the AI suspected group [57.1%], and 29 in the non-AI group [58.0%]). The baseline serum cortisol level was 4.3 ± 1.5 μg/dL in the AI probable group, 7.1 ± 1.3 μg/dL in the AI suspected group, and 8.0 ± 0.4 μg/dL in the non-AI group (F = 2.6378, p = 0.0799). The baseline ACTH levels were 10.8 ± 3.5 pg/mL (2.0–17.9 pg/mL) in the AI probable group, 16.0 ± 3.0 pg/mL (8.0–27.7 pg/mL) in the AI suspected group, and 14.8 ± 1.1 pg/mL (2.0–41.8 pg/mL) in the non-AI group (F = 0.8948, p = 0.5032). The baseline ACTH levels among these three groups were lower than or within the reference range (Table 1).

Exogenous steroids were used in 12 patients, as shown in Table 1; 1 orally received 3 mg of prednisolone every other day for organized pneumonia, 3 received topical steroid for atopic dermatitis or eczema, and the 8 other patients used inhaled steroids for bronchial asthma and chronic obstructive pulmonary disease. Exogenous steroid use was seen in 2 (40.0%) of the AI probable group, 3 (42.8%) of the AI suspected group, and 7 (14.0%) of the non-AI group (χ² = 4.761, p = 0.0925) (Table 1). A
A hypoglycemic episode was only seen in three patients of the non-AI group. Hyponatremia was not found in any of the three groups. Eosinophilia was seen in one of the AI probable group and seven of the non-AI group (Table 1).

The baseline ACTH levels among these three groups did not differ markedly. However, those values of baseline ACTH were lower than the reference or below of the reference range in all groups. The basal serum cortisol levels of the AI probable group were slightly lower than in the other two groups.

### Discussion

No reports have described the prevalence of AI among patients presenting with fatigue in the Department of Psychosomatic Medicine.

In this study, depression was diagnosed in almost half of patients presenting with fatigue. Regardless of the presence of depression, roughly 20% of patients met the criteria of AI (a serum cortisol level of <18 μg/dL at 30 or 60 min in response to 250-μg synthetic ACTH) [9]. Furthermore, 8.0% of these patients had a peak serum cortisol level <15 μg/dL, which is usually considered to indicate the possibility of primary AI [9]. This prevalence of possible or suspected AI among patients presenting with fatigue seems to be higher than would otherwise be expected, and no other studies have reported similar findings.

According to a previous report from the Netherlands, patients presenting with fatigue were diagnosed with musculoskeletal problems (19.4%), psychological or social problems (16.5%), or issues of the digestive system (8.1%), nervous system (6.7%), and respiratory tract (4.9%). However, none were diagnosed with AI [12].

When a physician evaluates a patient presenting with fatigue, it is recommended that AI be considered as a potential diagnosis in general. The diagnosis of AI is often difficult and starts when a physician suspects AI based on common symptoms [8].

Neither hyponatremia, hypoglycemia, nor eosinophilia was observed in the possible AI group, which includes the AI probable group and the AI suspected group, in this study. Indeed, hyponatremia, mild hypoglycemia, and eosinophilia were seen in 57%–88%, 87%, and 17% of primary AI cases in the emergency setting, respectively, in the literature [13]. Although the patients in this study complained of fatigue, they were not in an emergency setting, so the difference in the situation may have contributed to the different results observed for hyponatremia, hypoglycemia, and eosinophilia.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>AI probable group (n = 5)</th>
<th>AI suspected group (n = 7)</th>
<th>non-AI group (n = 50)</th>
<th>F or χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2 (40.0%)</td>
<td>2 (28.5%)</td>
<td>15 (30.0%)</td>
<td>0.230</td>
<td>0.6914</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.8 ± 9.4</td>
<td>42.8 ± 7.9</td>
<td>44.0 ± 2.9</td>
<td>0.1024</td>
<td>0.9028</td>
</tr>
<tr>
<td>Duration of fatigue (months)</td>
<td>20.3 ± 16.2</td>
<td>37.7 ± 13.6</td>
<td>14.7 ± 5.1</td>
<td>1.2516</td>
<td>0.2935</td>
</tr>
<tr>
<td>PS</td>
<td>2.2 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>0.7009</td>
<td>0.5002</td>
</tr>
<tr>
<td>BDI</td>
<td>12.6 ± 5.6</td>
<td>13.5 ± 4.4</td>
<td>16.4 ± 1.7</td>
<td>0.3439</td>
<td>0.7113</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (80.0%)</td>
<td>4 (57.1%)</td>
<td>29 (58.0%)</td>
<td>0.935*</td>
<td>0.6265</td>
</tr>
<tr>
<td>Trauma stress</td>
<td>2 (40.0%)</td>
<td>2 (28.5%)</td>
<td>11 (22.0%)</td>
<td>0.885*</td>
<td>0.6423</td>
</tr>
<tr>
<td>Hypoglycemic episode</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (6.0%)</td>
<td>0.757*</td>
<td>0.6850</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.000*</td>
<td>1.0000</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1 (20.0%)</td>
<td>0 (0.0%)</td>
<td>9 (18.0%)</td>
<td>1.531</td>
<td>0.4651</td>
</tr>
<tr>
<td>Steroid user</td>
<td>2 (40.0%)</td>
<td>3 (42.8%)</td>
<td>7 (14.0%)</td>
<td>4.761</td>
<td>0.0925</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical steroids</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled steroids</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal serum cortisol (μg/dL)</td>
<td>4.3 ± 1.5</td>
<td>7.3 ± 1.3</td>
<td>8.0 ± 0.4</td>
<td>2.6378</td>
<td>0.0799</td>
</tr>
<tr>
<td>Basal plasma ACTH (pg/mL) (interval)</td>
<td>10.8 ± 3.5 (2.0–17.9)</td>
<td>16.0 ± 3.0 (8.0–27.7)</td>
<td>14.8 ± 1.1 (2.0–41.8)</td>
<td>0.6948</td>
<td>0.5032</td>
</tr>
</tbody>
</table>

* indicates χ² analysis
PS, performance status; BDI, Beck depression inventory; AI, adrenal insufficiency
When patients present with fatigue, we should also consider myalgic encephalitis/chronic fatigue syndrome (ME/CFS). The new criteria of the Institute of Medicine define ME/CFS [14], as a substantial reduction or impairment in the pre-illness level of occupational, educational, social, or personal activities that persists for more than six months and is accompanied by fatigue, which is often profound, is of new or definite onset, and is not the result of ongoing excessive exertion, and is not substantially alleviated by rest [13]. In general, patients with ME/CFS have hypocortisolemia at baseline. However, the response to synthetic ACTH among these patients varies [15]. A small dose of steroid might improve the symptoms in patients with ME/CFS [16]. Therefore, the relationship between ME/CFS and AI remains unclear.

Patients with possible AI in this study all had low values or values within the reference range for plasma ACTH levels. Therefore, AI in this study might be central AI which means pituitary AI (including ACTH deficiency syndrome) or hypothalamic AI not rather than obvious primary AI.

According to the guide to diagnosis and treatment of ACTH deficiency from Japan Endocrine Society [17], the definite diagnosis needs 4 laboratory data including 1) low to lower normal levels of serum cortisol, 2) the decreased excretion of urinary free cortisol, 3) low to normal levels of plasma ACTH and 4) decreased response of plasma ACTH to CRH or insulin tolerance test (ITT), in addition to one of symptoms including of general fatigue, anorexia or digestive symptoms. However, the diagnostic criteria of hypothalamic AI from Japan Endocrine Society did not established so far.

Recently, Yamamoto [18] proposed the concept of latent primary AI. The baseline cortisol levels and ACTH profile of latent primary AI are almost the same as those of possible AI. Latent primary AI as proposed by Yamamoto [18] shows no obvious symptoms under a stress-free conditions and apparent symptoms under stressed conditions, along with a low response of cortisol to the rapid ACTH test. However, while, the concept of latent primary AI is attractive, unfortunately, Yamamoto [18] did not describe mention the difference between latent primary AI and central AI, especially that of hypothalamic origin. It is therefore difficult to differentiate latent primary AI and hypothalamic AI.

In Korea, another far-East Asia country like Japan, primary AI patients are rare, with central AI being more prevalent [19]. The causes of central AI are diverse, and include genetic, congenital, tumoral, iatrogenic, infiltrative, inflammatory, and miscellaneous causes [20].

Among these causes, exogenous steroids, including inhaled, topical, and intranasal agents, are common causes of central AI. In the present study, exogenous steroid use was more frequent in the AI probable group (40.0%) and the AI suspected group (42.8%) than in the non-AI group. The use of exogenous steroids might contribute, at least in part, to possible AI. Another potential cause of possible AI may have been chronic stress, such as chronic depression and repeated stressful traumatic life events, which eventually cause the hypothalamic pituitary-adrenal (HPA) axis to move from an over-responsive system to one that is under-responsive or non-responsive [21]. To clarify the underlying cause of possible AI in this study, the CRH test and ITT should have been conducted in order to determine whether the mechanism; was primary or central AI.

We must therefore take a thorough history concerning the use of exogenous steroids for issues such as bronchial asthma, atopic dermatitis, and rheumatoid arthritis in patients presenting with fatigue [22]. Furthermore, we must determine whether or not psychological factors play a role in central AI.

The subjects in the present study had experienced fatigue for over two weeks. Half of the subjects had depression, regardless of possible AI. Our depressive patients did not have hypercortisolemia, which has usually been documented in the literature [23]. Recent studies have described two types of HPA axis activations; melancholic depression as hyperactivation and atypical depression as hypoactivation. These phenomena might be related to elevated CRH or AVP levels [24].

Two-thirds of cases of fatigue in patients visiting our Department of Psychosomatic Medicine were attributed to possible AI or depression. However, the remaining one-third of cases of fatigue could not be attributed to either of these two causes.

Regarding the limitations associated with this study, the present study was only performed at a single center, so we should evaluate the prevalence of possible AI among patients presenting with fatigue at multiple centers. The CRH test and ITT to assess the HPA were not performed in this study; these two tests would help clarify the mechanism underlying the possible AI in patients complaining of fatigue.

Furthermore, the baseline pituitary hormones were measured in some but not all patients in the present study. The relationship of other hypothalamic or pituitary hormone deficiencies in our patients with probable or suspected AI was also not evaluated, which has limited our findings.

**Conclusion**

Depression was diagnosed in almost half of patients presenting with fatigue at the psychosomatic medical
Regardless of the presence of depression, roughly 20% of patients met the criteria of AI. Approximately 40% of possible AI has used exogenous steroids such as inhaled steroids in the past. However, the etiology of remaining 60% of possible AI was unknown. The CRH test and ITT to assess the HPA were not performed in this study; these two tests would help clarify the mechanism underlying the possible AI in patients complaining of fatigue. Furthermore, the baseline pituitary hormones were measured in some but not all patients in the present study. The relationship of other hypothalamic or pituitary hormone deficiencies in our patients with possible AI was also not evaluated, which has limited our findings.

**Conflicts of Interest**

None of the authors have any potential conflicts of interest associated with this research.

**References**