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Idiopathic combined adrenocorticotropin and growth hormone deficiency mimicking chronic fatigue syndrome

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TITLE OF CASE

Idiopathic combined adrenocorticotropin and growth hormone deficiency mimicking chronic fatigue syndrome

SUMMARY

A 42-year-old man who had suffered from severe fatigue for 5 years was diagnosed as having chronic fatigue syndrome (CFS) and fibromyalgia. Endocrinological workup using combined anterior pituitary function tests showed that the patient had adrenocorticotropin (ACTH) deficiency, with a normal pituitary MRI. Treatment with a physiologic dose of oral hydrocortisone replacement physically ameliorated his general fatigue. A secondary workup using a growth hormone-releasing peptide-2 (GHRP-2) test revealed that he also had growth hormone (GH) deficiency, and GH replacement therapy was started. His muscle pain and depression were improved by the therapy. Here we present a rare case of combined deficiency of ACTH and GH in a middle-aged man with severe general fatigue. This case report aims to raise awareness of combined deficiency of ACTH and GH as a differential diagnosis of CFS and its mimics.

BACKGROUND

Adrenocorticotropin (ACTH) deficiency is well described as isolated ACTH deficiency (IAD). IAD is characterized by secondary adrenal insufficiency with low levels of ACTH and serum cortisol but normal levels of other pituitary hormones and a normal pituitary structure on radiological imaging. IAD was first reported by Steinberg in 1954.[1] Over 300 cases of IAD were reported between 1969 and 1994 in Japan, and an increasing number of cases have been reported since then.[2] The prevalences of diagnosed cases have been reported to be 1.91/1 000 000 in Miyazaki Prefecture, 7.3/1 000 000 in Tokushima area and 3.8/1 000 000 in Chuetsu district in Japan.[3 4] Adrenal deficiency may result in lassitude, fatigue, anorexia, weight loss, myalgia, and arthralgia.[2] IAD can be caused by an autoimmune mechanism by anti-pituitary antibodies, ACTH-producing cell depletion, and lymphocytic infiltration into the anterior pituitary gland. However, these have not been proven in many cases. As one of the congenital factors, it has been revealed that *TPIT* mutation can cause IAD.[5] Congenital hypopituitarism has been shown to be related to pituitary stalk interruption syndrome, in which several transcriptional factor genes are mutated.[6] On the other hand, it is thought that an autoimmune mechanism is involved in the etiology of IAD because one-third to half of the cases of IAD are associated with autoimmune diseases such as Hashimoto's disease.[7 8] Other etiologies include post-traumatic ACTH deficiency, Sheehan's syndrome, radiation and chronic opiate use.[9]

Some patients with ACTH deficiency have shown impairment of growth hormone (GH) secretion, which normalized after glucocorticoid replacement therapy.[10 11] It has been reported that glucocorticoids have long-term stimulatory effects on growth hormone synthesis, improve the sensitivity to GH-releasing hormone and control GH gene transcription in human somatotrophs.[12]

In this report, we present a case of combined deficiency of anterior pituitary hormones (ACTH and GH) in a middle-aged man with severe general fatigue.

CASE PRESENTATION

A 42-year-old man with a history of severe generalized fatigue for five years was diagnosed with chronic fatigue syndrome (CFS) and fibromyalgia. Prior to his diagnosis, he was able to work as a cleaner. However, he stopped working because of fatigue. He also complained of muscle pain, loss of appetite and sleep disturbances. His fatigue worsened gradually, prompting his referral from a pain clinic to our general medicine department for further evaluation. His past medical history was significant for inguinal hernia repair fifteen years ago. He had no relevant family history. He had no history of glucocorticoid treatment and no use of opiates.

He was a former smoker (18 pack years quitting at the age of 38 years) but denied a history of alcohol use. His home medication included occasional use of nonsteroidal anti-inflammatory medication, loxoprofen. He had a negative history of opiate use. Additionally, he was depressed with an SDS (self-rating depression scale) score of 45 at arrival to our department and a score of 52 five years ago when he was diagnosed with CFS and fibromyalgia. The cut-off SDS score for a positive diagnosis is 39 and indicate greater depressive status.[13]

On examination, he was hemodynamically stable with a heart rate of 76 beats per minute and blood pressure of 121/76 mmHg. He weighed 63.9 kg and had a normal body mass index of 20.0 (kg/m^2). Examination of the skin was unremarkable for hyperpigmentation. He was well-hydrated. There was no thyromegaly. Musculoskeletal examination revealed tenderness in multiple muscle groups including the triceps, lumbar region, hip, and hamstrings.

INVESTIGATIONS *If relevant*

Laboratory data on presentation are shown in **Table 1**. Of significance, the patient had extremely low levels of ACTH, cortisol and IGF-I. Complete blood count and liver function tests were normal.

Table 1. Initial laboratory evaluation

Analyte	Result	Reference interval
Sodium (mmol/L)	139	138-145
Potassium (mmol/L)	3.9	3.6-4.8
Calcium (mg/dL)	9.0	8.8-10.1
Phosphate (mg/dL)	3.7	2.7-4.6
Magnesium (mg/dL)	1.7	2.0-2.5
Creatinine (mg/dL)	0.76	0.65-1.07
eGFR (mL/min/1.73 m2)	90.2	
Hemoglobin A1c (%)	5.1	4.9-6.0
Cortisol (μg/dL)	<1	4.5-21.1
ACTH (pg/mL)	<1.5	7.2-63.3
FT4 (ng/dL)	0.78	0.97-1.69
TSH (μU/mL)	10.8	0.33-4.05
FSH (mIU/mL)	8.9	1.3-17.0
LH (mIU/mL)	6.2	0.5-7.8
PRL (ng/mL)	46.4	3.0-17.3
Total Testosterone (ng/mL)	5.42	1.87-9.02
GH (ng/mL)	0.04	0-2.47
IGF-I (ng/mL)	46	93-259 (age/sex adjusted)[14]
Urinary Aldosterone (μg/day)	6.5	2-10
24-hour Urinary Free Cortisol (μg/day)	1.2	26-187
Anti-Thyroglobulin antibody	Positive	-
Anti-Thyroid Peroxidase antibody	Negative	-

Anti-Pituitary antibody	Negative	-

・eGFR, estimated glomerular filtration rate; ACTH, adrenocorticotrophic hormone; FT4, free thyroxine 4; TSH, thyrotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; GH, growth hormone, IGF-I, insulin-like growth factor I.
・Urinary free cortisol was measured when taking hydrocortisone at 5 mg/day.

An abdominal CT scan showed bilateral adrenal atrophy. Pituitary MRI sagittal and coronal views were unremarkable(**Figure 1**). Anterior pituitary hormonal evaluation showed no response of cortisol with ACTH. The ACTH level after CRH stimulation remained significantly low (up to 2.2 pg/mL) and cortisol secretion continued to be markedly suppressed (<1.5 μg/dL) (**Figure 2**). These results confirmed secondary adrenal insufficiency to be the underlying etiology. The evaluation also showed impaired secretion of GH (<9 ng/mL) in a growth hormone-releasing peptide-2 (GHRP-2) tolerance test (maximum GH level of 5.28 ng/mL; 30 min) (**Figures 3**). This result met the diagnostic criteria of GHD in Japan.[15] A secondary workup of the GHRP-2 test was performed six months after the first examination. These two GHRP-2 tests showed that GH secretion was not adequate despite hydrocortisone administration. Finally, we made a diagnosis of combined ACTH and GH deficiency.

DIFFERENTIAL DIAGNOSIS *If relevant*

A diagnosis of secondary adrenal insufficiency and adult growth hormone deficiency (AGHD) was made in this case. Other endocrine diseases that cause general fatigue have been reported to be Cushing's disease, hypo/hyperthyroidism, and diabetes mellitus.[16 17] The following findings also suggested that the aetiology of ACTH deficiency in this case was idiopathic: negative result for anti-pituitary antibody, normal level of IgG4 (24.4 mg/dL) and normal pituitary MRI. The possibility of sarcoidosis, granuloma, or histiocytosis was considered, but the findings indicated that such a possibility was unlikely.

TREATMENT *If relevant*

Treatment was initiated with hydrocortisone at 5 mg orally in the morning with dose escalation to 10 mg daily over a 3-month period. Therapy was continued for 6 months, and re-examination of the secretion of growth hormone showed that the level was still low (**Figure 3**). Due to the continuous low level of GH, we started treatment with somatropin at 0.6 mg per week one year after being diagnosed with IAD and AGHD.

OUTCOME AND FOLLOW-UP

Clinically, symptoms of general fatigue and muscle pain improved and his body weight increased from 63.3 kg to 74.7 kg during a period of 9 months after diagnosis of IAD. Furthermore, he had a more muscular physique, and his mood and endurance were improved after GH replacement therapy. His serum IGF-I level increased to 107 ng/mL and his body weight increased to 78.4 kg during a one-year period of treatment with somatropin (**Figure 4**). Furthermore, although his psychological status was depressive (self-rating depression scale: SDS of 45 points) before the replacement therapy, it improved to an SDS score of 38 points within 18 months after starting dual treatment.

DISCUSSION *Include a very brief review of similar published cases*

Most patients with primary adrenal insufficiency experience a nonspecific symptom of fatigue.[2] Fatigue combined with gastrointestinal or musculoskeletal complaints often leads to an incorrect diagnosis. One study showed that 20 percent of patients with primary adrenal insufficiency had symptoms for more than five years before diagnosis.[18]

Very low secretion of pituitary ACTH is well described as IAD. IAD is a rare clinical entity that is characterized by a low level of serum cortisol and decreased production of ACTH with normal secretion of other anterior pituitary hormones and normal pituitary imaging.[19 20] The etiologies of IAD remain unclear, but autoantibodies to pituitary cells were detected in some cases of IAD,[21 22] and the disease is presumed to be induced partially by an autoimmune mechanism such as lymphocytic hypophysitis.[23] A relationship between chronic thyroiditis (Hashimoto's thyroiditis) and IAD has also been reported.[7

24] Our case had a positive anti-TPO antibody, high level of TSH, and low level of free T4 before the hydrocortisone replacement therapy, indicating a possible relationship between IAD and the autoimmune process. Additionally, TSH can be mildly elevated (10.8 µU/mL at the initial evaluation) given that there is no physiological inhibitory effect of cortisol on TSH.[10] Our patient's TSH improved to 4.01 µU/mL without taking levothyroxine once his cortisol was replaced. Furthermore, although chronic opiate use is also an important etiology of IAD,[9] he had a negative history of opiate use.

Some patients with ACTH deficiency have shown impairment of GH secretion, which was normalized after glucocorticoid replacement therapy.[10 11] It has been reported that glucocorticoids have long-term stimulatory effects on growth hormone synthesis, improve the sensitivity to GRH and control GH gene transcription in human somatotrophs.[12] This phenomenon is described as Giustina's effect.[25] In our case, despite taking hydrocortisone for six months, the secretion of GH did not recover. One possible reason for this is that the long-term absence of ACTH and cortisol stimulus caused a dysfunction in secretion of GH from the pituitary.

In summary, we presented the clinical course of a middle-aged man who suffered from fatigue for five years and was finally diagnosed with combined ACTH and GH deficiency with a structurally normal pituitary gland on MRI. This combined pathophysiological status probably represented his physical and mental conditions. His physical general fatigue was improved with glucocorticoid and GH replacement therapy. Although ACTH deficiency is more common in older men, this case indicates the importance for physicians to consider the possibility of this rare but important disease in patients who have general fatigue.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

► Combined deficiency of ACTH and GH may mimic chronic fatigue syndrome.

► All doctors should check for evidence of ACTH and/or GH deficiency in patients who complain of fatigue to improve the timely diagnosis for this potentially serious but curable condition.

►GH replacement therapy may improve muscle pain, mood and endurance in a patient with deficiency of GH.

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FIGURE/VIDEO CAPTIONS

Figure 1. (**A**) Abdominal CT scan: Bilateral atrophic adrenal glands were shown by CT. MRI in sagittal (**B**) and coronal (**C**) views: No morphological changes in the pituitary gland were detected.
Figure 2. Anterior pituitary hormonal evaluation: Endocrine tests were performed using stimulations with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH) and growth hormone-releasing hormone (GRH).
Figure 3. Growth hormone responses to growth hormone-releasing peptide (GHRP)-2 stimulations. The dotted line represents the reference level of growth hormone secretion in growth hormone deficiency (9 ng/mL), which is a diagnostic criterion of severe GHD in Japan.
Figure 4. Clinical course and body images during replacement therapy.

PATIENT'S PERSPECTIVE

I appreciate having been diagnosed and successfully treated with hydrocortisone and somatropin, which improved my general fatigue. I am now feeling well enough to be able to work and am trying to find a job.

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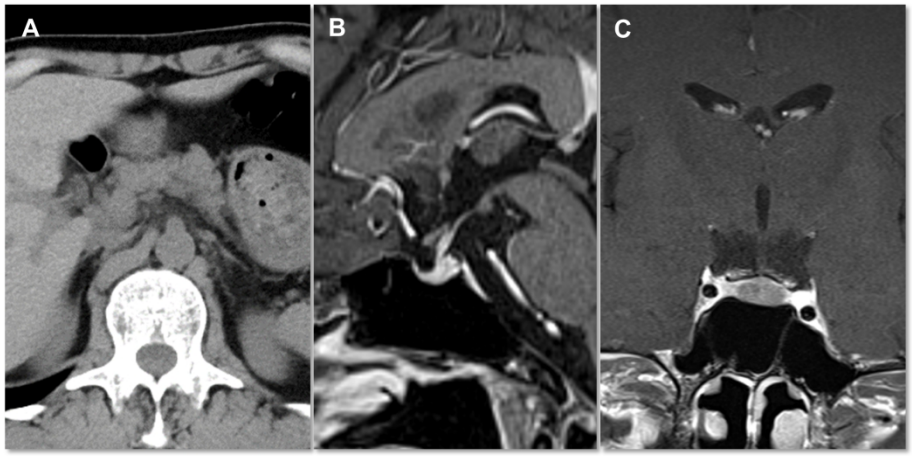
EXAMPLE OF A WELL PRESENTED CASE REPORT
Resection of a large carotid paraganglioma in Carney-Stratakis syndrome: a multidisciplinary feat

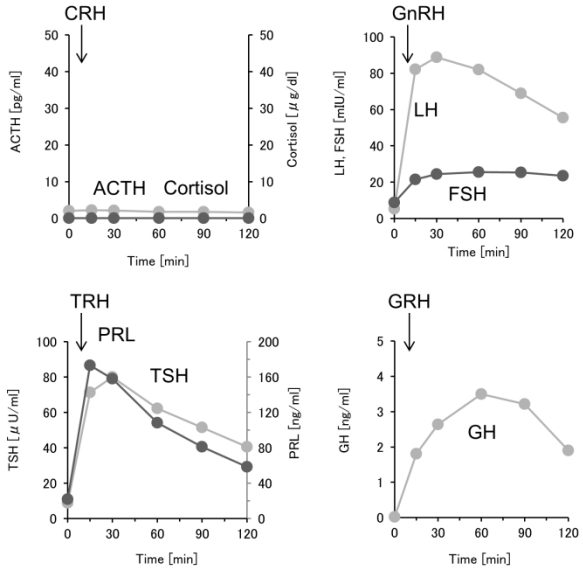
Figure 1.



(A) Abdominal CT scan: Bilateral atrophic adrenal glands were shown by CT. MRI in sagittal (B) and coronal (C) views: No morphological changes in the pituitary gland were detected.

254x190mm (300 x 300 DPI)

Figure 2.



Anterior pituitary hormonal evaluation: Endocrine tests were performed using stimulations with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH) and growth hormone-releasing hormone (GRH).

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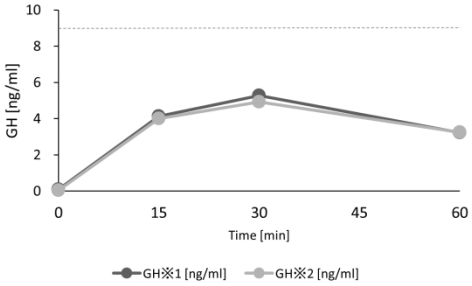
Figure 3.



Time [min]	0	15	30	60
GH※1 [ng/ml]	0.09	4.14	5.28	3.23
GH※2 [ng/ml]	0.05	4.00	4.93	3.24

※1 After two months when taking hydrocortisone
※2 After six months when taking hydrocortisone

Growth hormone responses to growth hormone-releasing peptide (GHRP)-2 stimulations. The dotted line represents the reference level of growth hormone secretion in growth hormone deficiency (9 ng/mL), which is a diagnostic criterion of severe GHD in Japan.

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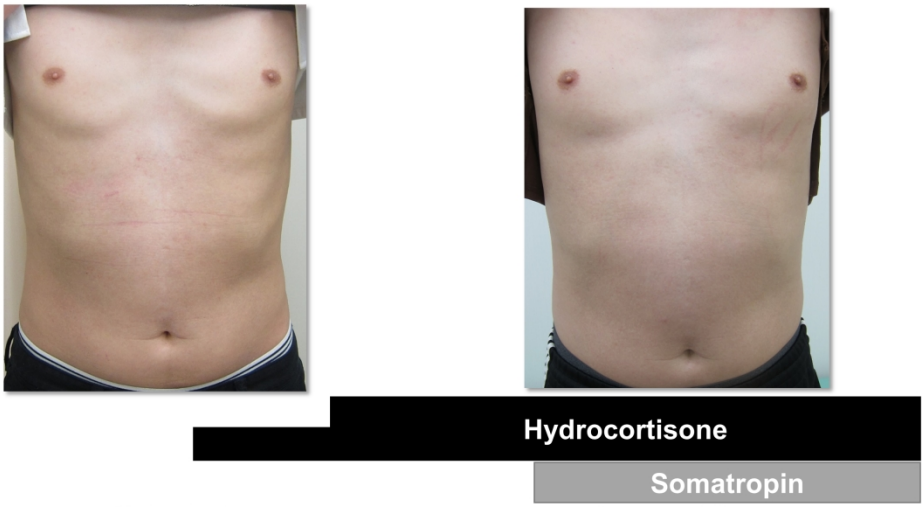
Figure 4.



Clinical course and body images during replacement therapy.

254x190mm (300 x 300 DPI)