Idiopathic combined adrenocorticotropin and growth hormone deficiency mimicking chronic fatigue syndrome

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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 hormone (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 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 hormone (ACTH) deficiency is well described as isolated ACTH deficiency (IAD). IAD is characterised 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 antipituitary 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 aetiology 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 aetiologies 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 normalised after glucocorticoid replacement therapy.10 11 It has been reported that glucocorticoids have long-term stimulatory effects on GH 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 generalised fatigue for 5 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 reported 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 medical history was significant for inguinal hernia repair 15 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 non-steroidal anti-inflammatory medication, loxoprofen. He had a negative history of opiate use. Additionally, he was depressed with a self-rating depression scale (SDS) score of 45 at arrival to our department and a score of 52 5 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 14

On examination, he was haemodynamically stable with a heart rate of 76 beats per minute and blood pressure of 121/76 mm Hg. He weighed 63.9 kg and had a normal body mass index of 20.0 kg/m². 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

Laboratory data on presentation are shown in table 1. Of significance, the patient had extremely

### Table 1. Laboratory data

| Parameter | Value |
|-----------|-------|
| Sodium | 138 mmol/L |
| Potassium | 4.5 mmol/L |
| Chloride | 106 mmol/L |
| Bicarbonate | 22 mmol/L |
| Calcium | 9.6 mg/dL |
| Phosphorus | 2.8 mg/dL |
| Glucose | 85 mg/dL |
| Hemoglobin | 13.5 g/dL |

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low levels of ACTH, cortisol and insulin-like growth factor I (IGF-I). Complete blood count and liver function tests were normal.

A CT scan of the abdominal showed bilateral adrenal atrophy. MRI sagittal of the pituitary and coronal views were unremarkable (figure 1). Anterior pituitary hormonal evaluation showed no response of cortisol with ACTH. The ACTH level after corticotropin-releasing hormone 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 aetiology. The evaluation also showed impaired secretion of GH (<9 ng/mL) in a growth hormone-releasing hormone-2 (GHRP-2) tolerance test (maximum GH level of 5.28 ng/mL; 30 min) (figure 3). This result met the diagnostic criteria of GH deficiency in Japan. A secondary workup of the GHRP-2 test was performed 6 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.

### 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   |                                 |
| Haemoglobin 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)²⁵    |
| 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 | –                              |

Urinary-free cortisol was measured when taking hydrocortisone at 5 mg/day.

ACTH, adrenocorticotropic hormone; eGFR, estimated glomerular filtration rate; FSH, follicle-stimulating hormone; FT4, free thyroxine 4; GH, growth hormone; IGF-I, insulin-like growth factor I; LH, luteinising hormone; PRL, prolactin; TSH, thyrotropin.
treatment with somatropin at 0.6 mg per week, 1 year after being seen (figure 3). Due to the continuous low level of GH, we started to examine the secretion of GH showed that the level was still low. The findings indicated that such a possibility was unlikely. Sarcoidosis, granuloma or histiocytosis was considered, but the negative result for antipituitary antibody, normal level of IgG4 confirmed the aetiology of ACTH deficiency in this case was idiopathic: ACTH is a non-specific hormone that is released in response to various stimuli, including stress, exercise, and inflammation. The possibility of IAD,20 21 and the disease is presumed to be induced partially by an autoimmune mechanism such as lymphocytic hypophysitis.22 A relationship between chronic thyroiditis (Hashimoto’s thyroiditis) and IAD has also been reported.23 Our case had a positive anti-thyroid peroxidase (TPO) antibody, high level of thyrotropin (TSH) and low level of free T4 before the hydrocortisone replacement therapy, indicating a possible relationship between ACTH deficiency 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.16 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 aetiology of IAD,24 he had a negative history of opiate use.

Some patients with ACTH deficiency have shown impairment of GH secretion, which was normalised after glucocorticoid replacement therapy.10 11 12 It has been reported that glucocorticoids have long-term stimulatory effects on GH synthesis, improve the sensitivity to GRH and control GH gene transcription in human somatotrophs.12 This phenomenon is described as Giustina’s effect.24 In our case, despite taking hydrocortisone for 6 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 5 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.

**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 I am trying to find a job.

**Learning points**

- Combined deficiency of adrenocorticotropic hormone (ACTH) and growth hormone (GH) may mimic chronic fatigue syndrome.
- All doctors should check for evidence of ACTH and/or GH deficiency in patients who report 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.

**Contributors** All authors contributed to the write-up of this case report. KT and KO provided clinical information and reviewed the final text. KT was also responsible for obtaining patient consent. KO and FO provided information relevant to the investigations. KT wrote the discussion. FO compiled and edited the final text.

**DISCUSSION**

Most patients with primary adrenal insufficiency experience a non-specific symptom of fatigue.1 The aetiologies of IAD remain unclear, but autoantibodies to pituitary cells were detected in some cases of IAD.20 21 and the disease is presumed to be induced partially by an autoimmune mechanism such as lymphocytic hypophysitis.22 A relationship between chronic thyroiditis (Hashimoto’s thyroiditis) and IAD has also been reported.23 Our case had a positive anti-thyroid peroxidase (TPO) antibody, high level of thyrotropin (TSH) and low level of free T4 before the hydrocortisone replacement therapy, indicating a possible relationship between ACTH deficiency 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.16 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 aetiology of IAD,24 he had a negative history of opiate use.

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