Paradoxical surge of corticotropin after glucocorticoid replacement in central adrenal insufficiency

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Abstract

A 78-yr-old man was admitted in emergency with fatigue, anorexia, vomiting, hypothermia (35.1 °C on a hot August day), hypotension (89/56 mmHg) and hyponatraemia (126 mEq/l). Plasma corticotropin and cortisol were severely depressed: 0.84 pmol/L and 33.1 nmol/L respectively (reference range, 1.5–13.9 pmol/L and 110–505 nmol/L, respectively). Thyroid stimulating hormone was low-normal and free-triiodothyronine and free-thyroxine were subnormal. Magnetic resonance imaging revealed swelling of the pituitary gland and the stalk. The patient recovered after glucocorticoid replacement (200 mg/day intravenous hydrocortisone on Day 1 followed by tapering). Central diabetes insipidus which had become apparent had been treated with 1-desamino-8-D-arginine vasopressin. A surge of corticotropin and cortisol, 19.4 pmol/L and 712.1 nmol/L respectively, was found on Day 5 when luteinizing hormone, follicle stimulating hormone, and testosterone were subnormal and prolactin was slightly elevated. Subsequently, corticotropin and cortisol levels normalized together with normalization of luteinizing hormone, follicle stimulating hormone, anti-diuretic hormone, thyroid stimulating hormone, prolactin, testosterone and thyroid hormone levels. Shrinkage of the pituitary gland occurred after one month. Serum immunoglobulin G4 was elevated (3.21 and 6.02 g/l at 1- and 3-month follow-ups respectively). In conclusion, a paradoxical surge of corticotropin after glucocorticoid replacement was observed in a patient with central adrenal insufficiency due to immunoglobulin G4-related hypophysitis. Surge of ACTH in central adrenal insufficiency after glucocorticoid replacement has rarely been reported, and this is the second such case report.

CASE REPORT

INTRODUCTION

Autoimmune hypophysitis has been recognized as an immunoglobulin G4 (IgG4)-related disorder (van der Vliet & Perenboom RM 2004; Yamamoto *et al.* 2006; Hori *et al.* 2010; Leporati *et al.* 2011; Umehara *et al.* 2012). Its clinical manifestations are diverse (Caturegli *et al.* 2005; Hamnvik *et al.* 2010; Rumana *et al.* 2010; Lupi *et al.* 2011), and diagnostic criteria have recently been proposed (Leporati *et al.* 2011). Spontaneous recovery of pituitary function (Imura *et al.* 1993) and/or recovery after glucocorticoid treatment (Imura *et al.* 1993; Yang *et al.* 1993; Yamagami *et al.* 2003; Caturegli *et al.* 2005; Miyake *et al.* 2006; Hamnvik *et al.* 2010; Rumana *et al.* 2010; Lupi *et al.* 2011) have been reported. In a single case of hypophysitis with central adrenal insufficiency (Hori *et al.* 2010), surge of ACTH has been found shortly after glucocorticoid replacement, and the authors speculated that it was due to resolution of inflammation by glucocorticoid (Hori *et al.* 2010).

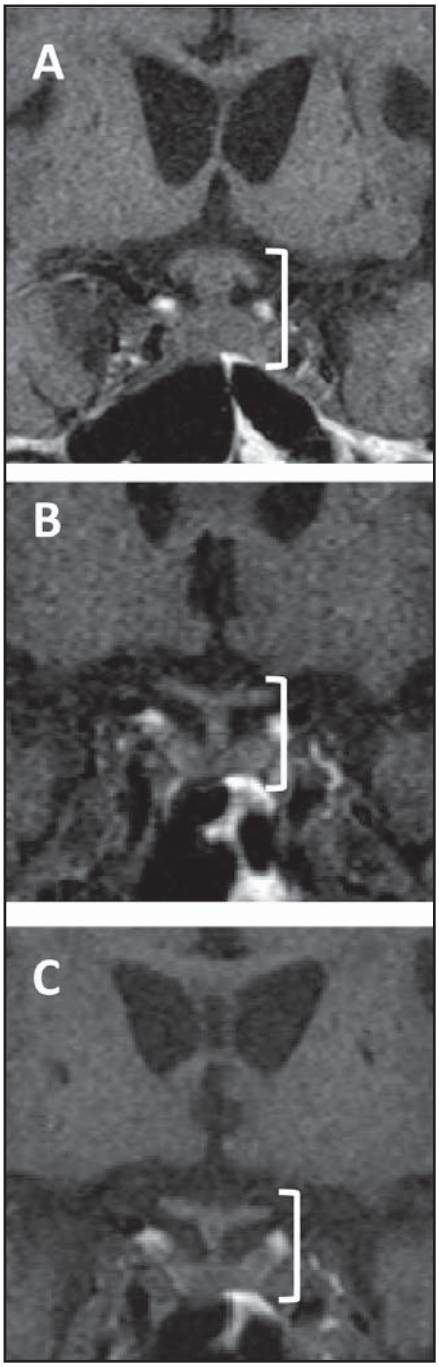

Fig. 1. Cranial MRI (T1-weighted images). There was diffuse swelling of the pituitary gland and the hypohyseal stalk (a white bracket) on admission (A). Shrinkage of the pituitary gland and the stalk was observed on Day 39 (B). Shape of the pituitary gland and the stalk was almost normal 4 months after admission (C).

CASE REPORT

A 78-yr-old man was admitted through the emergency department because he was unable to stand-up.

His type 2 diabetes had been treated with 5 mg glibenclamide for 8 years. He had developed lacunar infarction 7 years previously. For several days immediately prior to admission, he had experienced excessive fatigue and loss of appetite. On the day before admission, he had vomited undigested food. He had felt dizzy on the day of admission, and systolic blood pressure (BP) had been 80 mmHg at home.

Upon arrival, his level of consciousness was 13 on the Glasgow Coma Scale (E4V4M5) without focal neurological deficit. His height was 167 cm and body weight 57 kg. His body temperature was 35.1 °C (on a hot August day), BP 89/56 mmHg, pulse rate 76/min, arterial pH 7.446 and SpO_2 97% (with room air). The general laboratory data showed marked hyponatremia (126 mEq/L), with high-normal potassium concentration (4.6 mEq/L). The percent eosinophil count was 4.2% with the total white blood cell count being 4.98×10^9/l. Plasma and urine osmolarity were 258 and 302 mmol/kg H_2O respectively. Urinary sodium concentration was 67 mEq/L. Plasma glucose was 7.2 mmol/L, which was compatible with the diagnosis of type 2 diabetes. Magnetic resonance imaging (MRI) revealed symmetrical, diffuse enlargement of the pituitary gland and the hypophyseal stalk (Figure 1A).

He was admitted for treatment and further evaluation. A blood sample to determine corticotropin, cortisol, thyroid stimulating hormone (TSH), free-triiodothyronine (FT_3) and free-thyroxine (FT_4) was obtained. Immediately thereafter, 200 mg hydrocortisone was administered intravenously with saline during the initial 6 hours. Both orticotropin and cortisol values were later found to be severely depressed: corticotropin 0.84 pmol/L and cortisol 33.1 nmol/L (reference range, 1.5–13.9 pmol/L and 110–505 nmol/L respectively) (Table 1). FT_3 and FT_4 were subnormal (FT_3 3.9 pmol/L and FT_4 8.5 pmol/L with respective reference ranges of 4.00–7.85 pmol/L and 12.9–23.2 pmol/L) and TSH was low-normal (Table 1). Therefore, 25 μg L-thyroxine was given from Day 3. He continued to receive intravenous

hydrocortisone (200 mg/day on Day 2 and 100 mg/day from Day 3 to Day 5) and fluid supplement. Systolic BP was over 100 mmHg on Day 2 and thereafter, and body temperature normal (>36.5 °C) on Day 3 and thereafter, with his symptoms being dramatically improved.

A comprehensive endocrine evaluation was performed using a blood sample drawn on Day 5 at 0700 h (Table 1). On that day, the blood sample was taken before starting the administration of hydrocortisone. To our surprise, plasma corticotropin and cortisol concentrations were both markedly elevated: 19.4 pmol/L and 712.1 nmol/L respectively. Luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone were subnormal, whereas the prolactin level was slightly elevated (Table 1). Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) were within the normal range. FT_3 and FT_4 were subnormal with a normal level of TSH, as on Day 1, and the administration of 25 µg L-thyroxine was continued. Serum sodium concentration was as high as 152 mEq/L and plasma osmolarity 306 mmol/kg H_2O. BP was high normal, i.e., 153/111 mmHg. Plasma anti-diuretic hormone (ADH) concentration was not elevated, implying a defective response to hyperosmolarity/hypernatremia (Table 1). Plasma renin activity was 1.4 µg/L/hr (reference range, 0.3–2.9 µg/L/hr) and aldosterone was 0.17 nmol/L (reference range, 0.10–0.66 nmol/L).

After Day 6, intravenous hydrocortisone was further tapered (80 mg on Day 6 and 7, and 50 mg from Day 8 to 14). He had complained of excessive thirst, urine output had been over 4 liters/day, and serum sodium concentration had remained elevated. Central diabetes insipidus (DI) was diagnosed and treated with a nasal drip of 1-desamino-8-D-arginine vasopressin (dDAVP). Intravenous hydrocortisone was replaced with oral hydrocortisone (40 mg from Day 15 to 23, 30 mg from Day 24).

On Day 39, normalization of the shape of the pituitary gland with slight thickening of the stalk was found (Figure 1B). The physiologic posterior lobe brightness was not visible. Serum IgG4 was elevated (3.21 g/L, reference range 0.48–1.05 g/L), whereas anti-pituitary antibody (Komatsu *et al.* 1988) was negative. Anti-thyroglobulin and anti-thyroid peroxidase antibodies were also negative. The plasma level of pituitary hormones, thyroid hormones, IGF-1 and testosterone were all normal, except that cortisol was elevated and corticotropin was subnormal (Table 1): the patient took a morning dose (10 mg) of hydrocortisone and blood was sampled approximately 3 hours thereafter on this occasion. L-thyroxine was withheld and hydrocortisone continued at a dose of 15 mg.

Two months after admission, further improvement of pituitary function was indicated by progressive elevation of TSH, LH, FSH and testosterone (Table 1). The elevated cortisol and lowered corticotropin, in a blood sample taken after the morning dose of hydrocortisone, was unchanged. Three months after admission, we took a blood sample after withholding the morning dose of hydrocortisone and dDAVP. As shown, pituitary hormones, including corticotropin and cortisol, were all normal (Table 1). TSH, FT_4, LH, FSH and testosterone levels were in the mid-normal to high-normal range. Slightly elevated GH in the presence of normal IGF-1 was considered insignificant. By this time, IgG4 had risen still further (6.02 g/L). Four months after admission, the shape of the pituitary gland and the stalk was

Tab. 1. Laboratory data.

Measurement	Day 1	Day 5	Day 39*	2 months after admission*	3 months after admission	Reference range
Pituitary-adrenal axis						
Cortcotropin, pmol/L	0.84	19.40	1.12	0.90	3.98	1.5–13.9
Cortisol, nmol/L	33.1	712.1	772.8	698.3	361.6	110–505
Pituitaiy-thyroid axis						
TSH, mU/L	0.35	2.42	2.74	3.21	3.64	0.27–4.20
FT_3, pmol/L	3.94	2.80	4.40	4.47	4.67	4.00–7.85
FT_4, pmol/L	8.5	12.4	20.5	20.2	18.7	12.9–23.2
Pituitary-gonadal axis						
LH. IU/L	N.D.	0.63	2.79	3.02	4.55	0.7–5.72
FSH, IU/L	N.D.	0.91	6.35	5.42	7.87	2.00–8.30
Testosterone, nmol/L	N.D.	0.66	15.89	18.91	23.67	4.55–30.2
Osmoregulation						
ADH, pmol/L	N.D.	0.56	0.83	0.46	0.93	0.28–3.24
Na, mEq/L	126	152	138	137	135	135–147
Others						
PRL, nmol/L	N.D.	0.98	0.48	0.36	0.53	0.19–0.60
GH, µg/L	N.D.	0.42	0.93	0.66	1.86	0.17–1.00
IGF-1, µg/L	N.D.	84	167	130	156	75–218

TSH, thyroid stimulating hormone; FT_3, free triiodothyronine; FT_4, free thyroxine; LH, luteinizing hormone; FSH, follicle stimulating hormone; ADH, anti-diuretic hormone; PRL, prolactin; GH, growth hormone; IGF-1, insulin like growth factor-1; N.D., not determined. *, on these occasions, blood sampling was performed 3-4 hours after 10 mg hydrocortisone p.o. and a nasal drip of 5.0 µg 1-desamino-8-D-arginine vasopressin.

almost normal (Figure 1C) but the physiologic posterior lobe brightness was not visible.

DISCUSSION

The patient had central adrenal insufficiency due to IgG4-related hypophysitis (Leporati *et al.* 2011). Interestingly, we found a surge of corticotropin shortly after glucocorticoid replacement. For several days, we were ignorant of this surge as we waited to obtain the corticotropin and cortisol values from the laboratory, and we continued to administer what we considered was an appropriate amount of hydrocortisone on the basis of the clinical presentation and the laboratory data from Day 1. Subsequently, the glucocorticoid dosing was tapered. Under this circumstance, the surge of corticotropin was transient, and the plasma level of corticotropin settled down to within the low-normal range several months later.

In the literature (Imura *et al.* 1993; Yang *et al.* 1993; Yamagami *et al.* 2003; van der Vliet & Perenboom RM 2004; Caturegli *et al.* 2005; Miyake *et al.* 2006; Yamamoto *et al.* 2006; Hamnvik *et al.* 2010; Hori *et al.* 2010; Leporati *et al.* 2011; Lupi *et al.* 2011; Umehara *et al.* 2012), a paradoxical surge of corticotrophin after glucocorticoid replacement has been reported only once in a patient with very mild central adrenal insufficiency (Hori *et al.* 2010), in whom corticotropin rose from 7.0 to 31.5 pmol/L. We hypothesized that the phenomenon might be very rare or have gone mostly unnoticed because repetitive determination of pituitary function early in the course of treatment in this disorder is not a routine practice.

We considered two possible explanations for the surge of corticotropin. One was positive feedback regulation by glucocorticoid on the hypothalamic-pituitary axis, as demonstrated by Fehm and colleagues (Fehm *et al.* 1979; Peters *et al.* 2007). They hypothesized that positive feedback takes place through glucocorticoid binding to, and occupancy of, the brain mineralocorticoid receptor (MR), at low concentrations of glucocorticoid (Peters *et al.* 2007). Their hypothesis was constructed on the basis of data from patients with Addison's disease and adrenalectomized patients with Cushing disease (Fehm *et al.* 1979; Peters *et al.* 2007), in whom both cortisol and aldosterone were lacking. However, the situation in patients with central adrenal insufficiency is different in that the plasma concentration of aldosterone is usually normal or only slightly suppressed (current case, Hori *et al.* 2010), so that the brain MR should already have been occupied by aldosterone before glucocorticoid replacement. Therefore, in patients with central adrenal insufficiency, there is uncertainty with regard to the operation of the mechanism proposed by Fehm and colleagues (Fehm *et al.* 1979; Peters *et al.* 2007). On the other hand, direct enhancement of corticotropin precursor secretion in vitro by dexamethasone was reported in carcinoid tumor cells derived from a patient with Cushing disease (White *et al.* 2000). The other possibility was resolution of inflammation, i.e., hypophysitis, by hydrocortisone leading to improved functionality of the hypothalamic-pituitary axis, as suggested by Hori and colleagues (Hori *et al.* 2010). However, if this was the case, it is difficult to explain why glucocorticoid replacement had caused an early surge of corticotropin but not of the other pituitary hormones. In another case report of a patient with hypophysitis (Iida *et al.* 2003), not necessarily a surge but a clear-cut elevation of corticotropin, from 1.5 to 10.8 pmol/L, was observed after short-term administration of a small amount (15 mg) of hydrocortisone, which should have resulted in little anti-inflammatory action.

As has been reported (Iida *et al.* 2003; Huang *et al.* 2005), central DI masked by coexisting adrenal insufficiency has converted to overt DI after glucocorticoid replacement in our patient. In marked contrast to the brisk lowering of IgG4 after treatment with glucocorticoid seen in the previous case of IgG4-related hypophysitis (van der Vliet & Perenboom RM 2004; Hori *et al.* 2010; Leporati *et al.* 2011), we found progressive elevation of serum IgG4 at a 3-month follow-up. This finding suggested that immune abnormality had not subsided despite recovery of the pituitary function and shrinkage of the pituitary gland. A follow-up with particular attention being paid to the possible recurrence of hypophysitis (Hori *et al.* 2010), development of other IgG4-related disorders (Umehara *et al.* 2012), empty sella (Klein & Fehm 2005) and permanent hypopituitarism is under way.

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