Hypothalamic–pituitary–adrenal axis hypofunction after adrenocorticotropic hormone therapy

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Abstract

Purpose: To investigate the adverse effects of adrenocorticotropic hormone (ACTH) therapy on function of the hypothalamic–pituitary–adrenal (HPA) axis and the necessity of subsequent adrenocortical hormone replacement therapy (HRT).

Methods: We conducted a retrospective review of patients with epilepsy who received ACTH therapy and underwent assessment of HPA axis function.

Results: Six cases analyzed for hormones, including a symptomatic patient with HPA axis insufficiency (HPAI), were studied. Serum cortisol concentrations in the morning were at HPAI levels (<5.0 µg/dL) in three cases, at suspected HPAI levels (>5.0 and <13 µg/dL) in two cases, and normal in one case. However, in the corticotrophin-releasing hormone (CRH) test, while both serum cortisol and plasma ACTH levels were reactive in five cases, only one case exhibited lazy patterns in the time courses of serum cortisol and plasma ACTH levels. Consequently, all six patients who received ACTH therapy had some degree of HPA axis hypofunction for approximately 2-3 months after ACTH therapy and were treated with HRT.

Conclusion: Patients who receive ACTH therapy may be at risk of HPA axis hypofunction for a certain period and HRT may be recommended until their serum cortisol levels return to basal levels.
Introduction

Adrenocorticotropic hormone (ACTH) therapy is an effective treatment not only for West syndrome/infantile spasms (WS/IS) but also for other refractory epilepsy syndromes [1-3]. In Japan, ACTH therapy was started for patients younger than 1 year with WS/IS in 1958, and the regimen comprised intramuscular injections of 10 IU/dose of long-acting ACTH (ACTHAR-Z) daily for 2 weeks [4, 5]. After 1968, in many Japanese institutions, ACTHAR-Z was replaced with synthetic ACTH (tetraicosactide acetate with zinc suspended in emulsion; Cortrosyn® Z) (ACTH-Z). ACTH therapy was started at a dose of 0.25 mg (10 IU) ACTH-Z for patients under 1 year of age and 0.5 mg (20 IU) for patients over 1 year of age, once daily for 2 weeks and then once every other day for the next 2 weeks, twice weekly for 2 weeks, and finally once weekly for 2 weeks, with total doses of 6.25 and 13.5 mg, respectively [4-6]. Nonetheless, contrary to its proposed benefits, some adverse effects occurred during or after ACTH therapy. Hence, the dose of ACTH-Z was gradually reduced from 0.025 to 0.005–0.0125 mg/kg/dose once daily for 2 weeks and tapered in a phased manner [5-15]. Nonetheless, contrary to its proposed benefits, some adverse effects occurred during or after ACTH therapy. Hence, the dose of ACTH-Z was gradually reduced from 0.025 to 0.005–0.0125 mg/kg/dose once daily for 2 weeks and tapered in a phased manner [5-15]. Although the dose reduction minimized the adverse effects considerably, precaution is still needed for those adverse effects.

The adverse effects of ACTH therapy include infection, hypertension, bradycardia, hypertrophic cardiomyopathy, brain shrinkage, subdural effusion, irritability, hypokalemia, adrenocortical dysfunction, and suppression of the hypothalamic–pituitary–adrenal (HPA) axis or HPA axis insufficiency (HPAI) [6, 7, 12, 14]. Although HPAI is notably one of the most significant adverse effects, only four previous reports have demonstrated the adverse effects of ACTH therapy on the HPA axis [16-19]. Nevertheless, the assessment criteria for both the HPA axis function after ACTH therapy and adrenocortical hormone replacement therapy (HRT) have not been clearly evaluated or established.

Hence, to define the criteria, we conducted a retrospective study in patients with epilepsy who were treated with ACTH therapy and whose HPA axis function was evaluated. Our results alert the risk of potential HPAI after ACTH therapy and suggest the necessity of HRT until recovery of the HPA axis function.

Methods

Study design

This retrospective study was conducted by reviewing the medical records in a single institution; Saitama Medical University Hospital (Moroyama-machi, Saitama, Japan), between January 1, 2014 and April 30, 2016.

Patient demographics

We retrospectively enrolled patients who were diagnosed with WS/IS or refractory epilepsy and underwent evaluation of the HPA axis function during the study period. In this study, each patient was basically treated with intramuscular injections of 0.0125–0.025 mg/kg of ACTH-Z (tetraicosactide acetate; Cortrosyn® Z Intramuscular Injection; Daiichi Sankyo Co., Ltd., Tokyo, Japan) once daily for 14 consecutive days and then on alternate days for 14 days. However, the dose, duration, or both, were partially variable because some
patients needed extended treatment and/or dosage increase (Table 1).

**Evaluation of the HPA axis function (1): serum cortisol and plasma ACTH in the morning**

We assessed the primary function of the HPA axis by measuring the basal levels of both serum cortisol and plasma ACTH in the morning at 8:00–9:00 before and at various times after ACTH therapy: on the day before the first ACTH-Z injection (pre-ACTH), at 24 hours after the last injection (soon-after-ACTH), 3 days or later (post-ACTH), 1 month (1-month), 2 months (2-month), and 3 months (3-month) after the last ACTH-Z injection, where feasible. We classified the basal serum cortisol level as follows: (a) overt HPAI level, lower than 5 µg/dL; (b) normal level, higher than 13 µg/dL; and (c) suspected HPAI level, between 5 and 13 µg/dL [20]. When the pre-ACTH basal serum cortisol concentration was at suspected HPAI level without any signs of HPAI, it was considered as the normal level for that patient. Furthermore, at some point after ACTH therapy when the serum cortisol concentration increased to higher level than that at pre-ACTH, it was considered as the normal level for that patient, even if basal cortisol concentrations after ACTH therapy were still at suspected HPAI levels.

Each plasma ACTH level in the morning was evaluated with reference to the normal range in our institute: 7.4–55.7 pg/mL. In addition, when a patient was in abnormal condition such as symptomatic hypoglycemia and fever due to infection, the evaluation of the HPA axis was postponed until at least 3 days after resolution of the symptoms.

**Evaluation of the HPA axis function (2): Corticotrophin-releasing hormone challenge test**

The HPA axis function was evaluated by the corticotrophin-releasing hormone (CRH) test. In this test, patients were administered 5 µg/kg synthetic human CRH (Corticorelin; Human CRH “TANABE” Injection; Mitsubishi Tanabe Pharma Corporation Ltd., Osaka, Japan) intravenously in the morning. The CRH test was started between 08:00 and 09:00 a.m. on the third day or later after the last ACTH-Z injection (at the same time as “post-ACTH”). After CRH injection, blood samples were collected serially at 0, (15), 30, 60, 90, and 120 minutes for measurements of serum cortisol and plasma ACTH levels. In the CRH test, a serum cortisol increase to 20 µg/dL or higher is the criterion of normal HPA axis function [21-23].

**Research ethics**

This study was approved by the ethical committee of Saitama Medical University Hospital (No. 16-014-1). In addition, the hormonal examinations were conducted without neglecting the symptoms of HPAI. Informed consent was obtained orally from all evaluated patients’ parents.

**Results**

**Demographics of patients treated with ACTH therapy**

Table 1 shows patient demographics. Between January 1, 2014 and April 30, 2016, we identified 10 cases of ACTH therapy in our institution (10 ACTH therapies in nine patients). Of these, six cases (six ACTH therapies in five patients, three males and two females) were finally assessed for HPA axis
Cases 1 and 2 were the same patient who received ACTH therapy at two different periods. Patients’ ages at onset of epilepsy and at the start of ACTH therapy ranged from 5 days to 11 months and 4 months to 5 years, respectively. Treatment durations ranged from 28 to 39 days. Furthermore, the total doses of ACTH in each case ranged from 0.2625 to 0.5125 mg/kg. Some adverse effects caused by ACTH therapy were observed as follows: two cases of hypoglycemia (<70 mg/dL; symptomatic in Case 1 and asymptomatic in Case 5), one case (Case 3) of hypokalemia (<3.5 mEq/L), and two cases (Cases 2 and 5) of complicated viral infection. Moreover, five of six cases (Cases 1, 2, 3, 5, and 6) demonstrated brain shrinkage on brain computer tomography after ACTH therapy.

Only Case 1 had a symptomatic episode of hypoglycemia (plasma glucose, 48 mg/dL) and coma on the seventh day, in the morning after the last injection of ACTH-Z. Surprisingly, blood test at the same time revealed serum cortisol level of only 8 µg/dL despite such critical condition (ACTH was not measured at the same time).
**Basal levels of plasma ACTH and serum cortisol in the morning**

At pre-ACTH, while five cases examined (Cases 1, 2, 4, 5, and 6) had normal plasma ACTH levels (range: 21.1–31.1 pg/mL), two of the five cases (Cases 5 and 6) demonstrated suspected HPAI levels of serum cortisol (8.5 and 8.4 µg/dL, respectively) even before ACTH therapy. However, both cases were considered to be within the normal limit because of no sign of HPAI (Figure 1 and Table 2).

In addition, in the morning after the final injection (soon-after-ACTH), all four cases examined (Cases 2, 4, 5, and 6) had extremely high serum cortisol levels (range: 51.0–357.3 µg/dL) and markedly low plasma ACTH levels (range: 0.0–4.7 pg/mL; data not shown).

At post-ACTH, five of six cases (Cases 1, 2, 3, 4, and 6) had lower serum cortisol and plasma ACTH levels than those at pre-ACTH, whereas Case 5 had almost normal serum cortisol and plasma ACTH levels. In addition, three of six cases (Cases 1, 2, and 3) had overt HPAI levels of serum cortisol (4.7, 2.1, and 3.8 µg/dL, respectively), and two cases (Cases 4 and 6) had suspected HPAI levels (5.1 and 5.4 µg/dL, respectively).

During the period of post-ACTH to 3-month, two cases (Cases 4 and 6) had suspected HPAI levels of serum cortisol (between 13 and 5 mg/dL), and four cases (Cases 1, 2, 3, and 5) had suspected HPAI levels and also overt HPAI levels (<5 mg/dL) at least once. Finally, until 2-month or 3-month, serum cortisol levels in three cases (Cases 4, 5, and 6) almost reached the pre-

**Table 2. Evaluation of basic levels of serum cortisol and plasma ACTH in the morning and response to CRH test.**

| Case No. | Basal serum cortisol level and plasma ACTH level at each timing | Response to CRH test | ACTH cortisol |
|----------|---------------------------------------------------------------|-----------------------|---------------|
|          | pre-ACTH | post-ACTH | one-month | two-month | three-month |                          | ACTH cortisol |
|          | ACTH cortisol | ACTH cortisol | ACTH cortisol | ACTH cortisol | ACTH cortisol | ACTH cortisol |
| 1*       | Normal | Normal | Low | Low | Low | Normal | Borderline | Good | Good |
| 2        | Normal | Normal | Low | Low | Low | Normal | Borderline | Normal | Low | Poor | Poor |
| 3        | Low | Normal | Low | Normal | Low | Borderline | Normal | Borderline | Good | Good |
| 4        | Normal | Normal | Normal | Low | Normal | Normal | Normal | Good | Good |
| 5        | Normal | Normal | Normal | Normal | Low | Normal | Low | Normal | Normal | Good | Good |
| 6        | Normal | Normal | Normal | Low | Normal | Normal | Normal | Good | Good |

Serum cortisol level: Normal, > 13 µg/dL; Borderline (suspected HPAI level), 5-13 µg/dL; Low (overt HPAI level), < 5 µg/dL; a, symptomatic hypoglycemia; b, borderline level without any signs of HPAI; c, low basal plasma ACTH level for the cortisol level; d, borderline level but higher than that at pre-ACTH; Bold, Meeting criteria for the overt or suspected HPAI and hormone replacement therapy.

In addition, in the morning after the final injection (soon-after-ACTH), all four cases examined (Cases 2, 4, 5, and 6) had extremely high serum cortisol levels (range: 51.0–357.3 µg/dL) and markedly low plasma ACTH levels (range: 0.0–4.7 pg/mL; data not shown).

The CRH test conducted in all six cases at post-ACTH demonstrated transient CRH-reactive increases in both serum cortisol and plasma ACTH levels (Table 2). Five of six cases (Cases 1, 2, 3, 4, and 6) had both peak serum cortisol and plasma ACTH levels at 15 or 30 minutes after CRH injection, whereas Case 5 showed unique increase patterns in both serum cortisol and plasma ACTH levels.
In addition, five of six cases (Cases 1, 3, 4, 5, and 6) showed increases in serum cortisol level to higher than 20 µg/dL with corresponding elevations in plasma ACTH, whereas Case 2 demonstrated insufficient increases in both levels. In case 2, peak serum cortisol and plasma ACTH levels in the CRH test were 7.2 µg/dL at 30 minutes and 8.8 pg/mL at 15 minutes, respectively (Figure 2 and Table 2).

**Figure 2**: Serial levels of serum cortisol (A) and plasma ACTH (B) after a CRH injection. Five of six cases (cases 1, 2, 3, 4, and 6) had peak serum cortisol and plasma ACTH levels at 15 or 30 minutes after a CRH injection, whereas case 5 had unique increment patterns in both serum cortisol and plasma ACTH levels.

**Discussion**

Some adverse effects after ACTH therapy have been reported previously [8-12], especially when using the synthetic ACTH; ACTH-Z, which is the only formulation available for ACTH therapy in Japan and has much higher potential of adverse effects than natural ACTH. Hence, there is a need to study these effects in detail using synthetic
ACTH [24]. To the best of our knowledge, only four reports to date have evaluated the HPA axis function after ACTH therapy for WS/IS [16–19]. However, we cannot simply compare these studies with our patients because all the previous reports had different regimens of ACTH therapy and different hormonal evaluations (Table 3). Among the four studies, only Perheentupa et al. [17] used synthetic ACTH (Acortan prolongatum, Ferring, Malmö, Sweden) in ACTH therapy, which was different from the synthetic ACTH (ACTH-Z) that we used. Interestingly, they reported more patients with functional loss of the HPA axis than ours (five of nine cases vs. one of six cases) because they probably used a higher dose of synthetic ACTH for a longer duration [17] than we did, but we cannot simply compare the results of two studies. Similarly, since the total amounts of ACTH used in Cases 1, 2, and 3 were much larger than those in the other three cases (Cases 4, 5, and 6), the HPAI condition was more prolonged in Cases 1, 2, and 3 than in Cases 4, 5, and 6 (Table 1 and Figure 1A).

Our results show that good response in the CRH test after ACTH therapy does not exclude the risk of hypothalamic HPAI. The

| Study          | Ross [16] | Perheentupa et al. [17] | Rao & Willis [18] | Mytinger & Bowden [19] | Present study |
|----------------|-----------|-------------------------|------------------|------------------------|---------------|
| Year of publication | 1986      | 1986                    | 1987             | 2015                   | –             |
| No. of patients  | n = 5      | n = 10                  | n = 9            | n = 11 (ACTH 8, PSL 3) | n = 6         |
| Age at ACTH therapy | 8 m 8 y    | 5–22 m                  | 1.8–16 m         | 5–19 m                 | 4 m 5 y       |
| Type of ACTH     | Natural    | Synthetic               | Natural          | Natural                | Synthetic*    |
| Dose of ACTH / day | 1.1–9 IU/kg| 6.6–13.1 IU/kg          | 50–160 IU/m²     | 150 IU/m²              | 0.0125-0.025 mg/kg** |
| Duration of ACTH therapy (days) | 30–90     | 42                      | 30–66            | 29                     | 28–39         |
| Challenge tests for evaluation of HPA axis | Insulin injection | Combined vasoressin–synthetic ACTH | Metyrapone test | Synthetic ACTH or glucagon | CRH test |
| Time of hormonal evaluation | First day of ACTH or later | 3 days, and 2 wks after ACTH | 2 days after ACTH | 2–74 wks after ACTH | 3–16 days after last ACTH |
| HPA axis functional loss in challenge test after ACTH therapy | 1 of 5 cases | 5 of 9 cases | 5 (3*** of 9 cases) | 2 of 11 cases (ACTH 1, PSL 1) | 1 of 6 cases |
| Morning cortisol level (<5 µg/dL) | 1 of 5 cases (3.6 µg/dL) | Reduced | Not examined | 1 of 11 cases (PSL 1) | 4 of 6 cases |
| Morning cortisol level (>5 but <13 pg/mL) | - | - | - | - | 2 of 6 cases |

PSL, prednisolone; *, tetracosactide acetate; **, 1 mg of tetracosactide acetate equivalent to approximately 100 IU of ACTH [5]; ***, five patients with only low ACTH and three patients with both low ACTH and low cortisol
basal hormone levels in the morning should reflect the HPA axis function more evidently than the result of the CRH test. In addition, our result is useful for both patients and clinicians because measurement of a single serum cortisol level in the morning is much easier than the CRH test.

At post-ACTH, three cases (Cases 1, 2, and 3) had overt HPAI levels of both serum cortisol and plasma ACTH, and two cases (Cases 4 and 6) had suspected HPAI levels of serum cortisol and relatively overt HPAI levels of plasma ACTH considering the respective serum cortisol levels. This result indicated that these five cases (Cases 1, 2, 3, 4, and 6) should be diagnosed with hypothalamic (Cases 1, 3, 4, and 6) or pituitary (Case 2) HPAI, considering the hormone levels in the morning and the results of the CRH test (Table 2). Conversely, at 1-month or later, four cases (Cases 1, 2, 3, and 5) tended to have low cortisol levels together with low or normal levels of ACTH in the morning (Table 2). These cases should be diagnosed with adrenal HPAI rather than hypothalamic or pituitary HPAI, indicating that adrenal dysfunction may appear after hypothalamic or pituitary HPAI. Unlike steroid hormone therapy, the adrenal function can be maintained during and transiently after ACTH therapy. However, if hypothalamic or pituitary suppression is protracted, adrenal dysfunction may occur secondarily by the time both the hypothalamic and the pituitary functions have recovered. This suggests that good response in the CRH test relatively soon after the end of ACTH therapy (around 3 days) does not necessarily imply that the basal cortisol secretion will be functionally normal thereafter.

Ideally, hypothalamic HPAI should not be determined by the CRH test but should be diagnosed accurately by the insulin tolerance test. However, in our opinion, the insulin tolerance test should not be conducted in all patients after ACTH therapy because severe hypoglycemia may occur as a symptom of HPAI, as observed in Case 1. Streten et al. [25] reported that cortisol secretion should be stimulated and serum cortisol level should be elevated to higher than 18 µg/dL in normal HPA function when exposed to a severe hypoglycemic condition with blood glucose lower than 70 mg/dL, especially when the maximum level is lower than 45 mg/dL. However, Case 1 had a serum cortisol level of only 8.2 µg/dL even in a state of severe hypoglycemia (plasma glucose 48 mg/dL) despite having a normal result in the CRH test (unfortunately, plasma ACTH was not examined).

Furthermore, poor reactive secretions of both ACTH and cortisol in the CRH test may indicate hypofunction of the pituitary gland. As discussed earlier, Cases 1 and 2 were the same patient and this patient had the second ACTH therapy as “Case 2” at 6 months after the last injection of the first ACTH therapy (Case 1). Upon exposure to repeated ACTH therapies, not only the function of the hypothalamus but also the responsiveness of the pituitary gland may have worsened. In addition, the total amount of ACTH-Z may be related to the HPA axis function after ACTH therapy. With the exception of Case 5, the three cases (Cases 1, 2, and 3) that were administered 0.025 mg/kg/dose of ACTH-Z had prolonged HPA axis hypofunction, whereas the cases administered a lower dose of 0.125 mg/kg/dose (Cases 4 and 6) showed mild effect and early recovery of the morning corti-
sol level. However, further evaluation is warranted in the future, because we only examined six cases.

To specifically manage HPAI, we treated all six cases with 7 mg/m²/day of hydrocortisone (HDC) in three divided doses as daily HRT for 2 to 3 months soon after the evaluation of the HPA axis function. As the replacement dose of HDC was determined in amounts slightly higher than the daily cortisol production level of 5.7 mg/m²/day, the HRT should have a low potential for adverse influence on the residual HPA axis hypofunction even if the HPA axis is not affected by ACTH therapy [26]. Therefore, to avoid symptomatic HPAI, we recommend administration of a physiological amount of HDC for HRT at a dose of 7 or 8–10 mg/m²/day in three divided doses when cortisol measurement in the morning after ACTH therapy indicates a level of suspected HPAI, as mentioned in another report of HRT for post-prednisolone therapy [23].

Since most of the patients given ACTH therapy had no HPAI-related symptom, many clinicians do not always pay attention to this adverse effect. However, our results indicate that some patients receiving ACTH therapy may be at risk of HPAI for a few months after ACTH therapy. Hence, we recommend evaluation of the HPA axis function by assessing serum cortisol level in the morning, which is the easiest way to estimate adrenal function. If the serum cortisol level is above 5 but below 13 µg/dL, the possibility of HPAI cannot be ruled out; and if the level is below 5 µg/dL, the patient should be diagnosed with subclinical HPAI. Although it may seem to be an overestimation, this assumption is reasonably safe for asymptomatic patients. Therefore, to avoid symptomatic HPAI, we recommend HRT using a physiological amount of HDC for 2 to 3 months until recovery of the morning cortisol level, especially when the serum cortisol level in the morning on the third day or later after ACTH therapy is less than 13 µg/dL.

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Conflict of interest
Toru Kikuchi has potential conflict of interest to disclose as follows: honoraria for lectures given by Sanofi K.K. This disclosed COI is not related to this study at all. Yuichi Abe, Kaori Sassa and Hideo Yamanouchi have no potential conflicts of interest associated with this study.

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