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Effect of ACTH-induced hypercortisolemia on the EEG in patients with stress-related epilepsy

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Abstract

Purpose. We assess the effect of acute hypercortisolemia induced by ACTH stimulation on seizures and EEG interictal spike activity in patients with localization-related epilepsy (LRE) and stress-related seizures.

Methods. Seven patients (3 males, 4 females) with LRE and stress-related seizures were studied. All patients underwent ACTH stimulation with 0.25–0.75 mg Cosyntropin intravenously at 8 AM. Serum cortisol and ACTH levels were monitored half- to one-hourly for 4 to 6 hours. Video/EEG monitoring was also performed.

Results. ACTH injection induced hypercortisolemia in all patients. Hypercortisolemia was not associated with seizures or interictal spike facilitation in any patient. Two patients experienced seizures on the day of ACTH injection, one 8 hours after and another 15 and 12 hours after the injection, during a period when their cortisol levels had returned to normal.

Conclusion. No reproducible interictal EEG changes occurred in any of the patients following ACTH injection.

Keywords: Epilepsy; Seizures; Stress; Cortisol; Neurosteroids; Adrencorticotrophic hormone; Cosyntropin; Hypercortisolemia; Epileptiform discharges

1. Introduction

Stress is a common seizure precipitant in patients with epilepsy [1,2]. Pathophysiology of seizure facilitation by stress is unknown. In animal seizure models, cortisol exerts a proconvulsant effect [3]. In the present pilot study, we examined the hypothesis that acute elevation of cortisol secretion increases neuronal excitability in patients with stress-related epilepsy. We did so by investigating the effect of ACTH-induced acute hypercortisolemia on seizures and on EEG interictal spike activity in patients with localization-related epilepsy and stress-related seizures.

2. Methods

2.1. Subjects

Seven patients (three males, four females; age range, 13–45) with localization-related epilepsy (LRE) (six with temporal lobe epilepsy [TLE], one with frontal lobe epilepsy [FLE]) with subjectively perceived stress-related seizures underwent an ACTH stimulation test (Cosyntropin, Organon Inc.). All patients had refractory epilepsy. Two of seven patients were on antiepileptic drug (AED) monotherapy with partial seizure control. The remaining patients were taking two or three AEDs (Table 1). One patient had a vagal nerve stimulator in

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Table 1
Clinical and EEG characteristics of the patients

Patient	Sex	Age	Percentage of seizures related to stress (%)	Stress–seizure latency	Seizure Local	Spike change after ACTH	Seizures after ACTH (h/day)	Seizure cause[a]	AEDs[b]	Other medicines[b]	Duration of EEG monitoring before ACTH (days)	Duration of EEG monitoring after ACTH (days)
1	F	30	75	5–30 min	LT	–	+ (Days 3–5)[c]	Crypto	Cbz, Lm	Prozac, T_4	2	5
2	F	39	75	2 h	LT	+	+ (15 h)	Head trauma	Gbp, Lev, Zon	—	3	3
0.25 mg[d]										Zoloft	6	3
0.75 mg[d]						–	+ (12 h)					
3	F	28	50	Hours	BT, l > r	–	–	Crypto	Tpm, Lm, Lev	Depoprovera	1	1
4	F	16	25	Hours	RF	–	–	ICH	Tpm	Leupro, Progest	1	1
5	M	45	75	5 min	RT	–	–	Crypto	Cbz,Vpa	Zyprexa, Serzone	1	1
6	M	42	50	30–60 min	BT, r > l	–	–	Crypto	Tpm, Lev, Vpa, VNS	Haldol, Cogentin	1	6
7	M	13	75	30 min	RT	–	+ (8 h)	SWS	Oxc	Verapamil	2	1

[a] Crypto, cryptogenic; ICH, intracranial hemorrhage; SWS, Sturge Weber syndrome.
[b] Cbz, carbamazepine; Lev, levetiracetam; Lm, lamotrigine; Leupro, leuprolide; Oxc, oxcarbazepine; Progest, progesterone; Tpm, topiramate; T_4, synthroid; Vpa, valproic acid; VNS, vagal nerve stimulator; Zon, zonisamide.
[c] Seizures occurred after AED withdrawal.
[d] 0.25 and 0.75 Cosyntropin injection.

place. AEDs remained unchanged for 1 month before the injection and for at least 2 days after the injection. In four of seven patients, video/EEG monitoring was done as the first part (Phase 1) of presurgical evaluation for refractory epilepsy. Also in these patients, AEDs remained unchanged for at least 2 days after the ACTH injection.

Patients completed a questionnaire concerning the frequency and timing of seizure occurrence after stressful events or after a perceived change in stress level. Five of seven patients completed the questionnaire on three or more occasions, separated by at least 2 weeks. Greater than 25% of all seizures followed a perceived change in stress level in all patients. In six of seven patients, 50% of seizures followed stress (Table 1). Stress-related seizures occurred within minutes to hours of a change in stress level (Table 1).

2.2. Intervention/procedure

Patients were tested with the standard 0.25 mg Cosyntropin dose used for clinical testing of hypocortisolemia. Because there was an indication that one patient's EEG changed with this dose, this patient was retested 4 months later with a higher dose of 0.75 mg. Two of the women tested were amenorrheic at the time of testing (causes of amenorrhea: Depo-Provera, leuprolide). In the other two women, ACTH was administered on Menstrual Cycle Day 3. An intravenous cannula was placed 12 hours before injection. Blood was collected every 30 minutes for 2 hours after the injection, then every hour for another 4 to 6 hours.

2.3. Evaluations

All subjects underwent brain MRI. Serum was analyzed for cortisol and ACTH. In addition, in three patients, serum was analyzed for other adrenal steroids, namely, progesterone, 17α-hydroxyprogesterone, and dehydroepiandrosterone sulfate. Long-term video/EEG monitoring was performed starting at least 1 day before to 1 to 6 days after the injection. Minisphenoidal electrodes were used in addition to standard scalp electrodes in five of seven patients; Two patients had regular sphenoidal electrodes. Sphenoidal electrodes were placed at least 20 hours before the ACTH injection. Spikes were counted for 8 hours from 8 AM to 4 PM on the day before and the day of ACTH injection. Student's paired t test was used to analyze the difference. Daily seizure occurrence was charted for at least 7 days before ACTH injection and for 7 days after ACTH injection. The probability of a seizure occurring on the day after ACTH injection was determined by calculating the Poisson distribution of daily seizure occurrence. Significance was set at $P \leqslant 0.05$.

The protocol was approved, inclusive of informed written consent, by Beth Israel Deaconess Medical Center (Boston, MA, USA) IRB committee (IRB No. 98-1024).

3. Results

Two patients experienced a seizure on the day of ACTH injection. One was a 13-year-old boy who experienced a partial complex seizure with a right temporal EEG onset 8 hours after injection. Serum cortisol level was low (3 μg/dl) at that time, and had been low for 3 hours. Dehydroepiandrosterone sulfate (DHEAS), another neuroexcitatory steroid, was likewise low (49 μg/dl). He also had had one seizure 2 days before the injection out of 7 days of baseline seizure charting, making his seizure occurrence on the day of injection a statistically nonsignificant event ($P = 0.13$, Poisson distribution). There was no change in his infrequent right midtemporal interictal spikes on the day of injection compared with spikes on 2 days two before injection. A second patient, a 39-year-old woman who had spread interictal discharges, had a partial complex seizure with a left temporal electrographic focus 15 hours after the injection of 0.25 mg Cosyntropin. Serum cortisol was not measured at that time, but had returned to normal (16.8 μg/dl; normal <20 μg/dl at 8 AM, >4 μg/dl at 4 PM) when last measured 6 hours after injection. She had daily seizures from 2 days before to 3 days after ACTH injection, out of 7 days of baseline seizure charting ($P = 0.24$, Poisson distribution, for nonrandom seizure occurrence on the day of ACTH injection). When the test was repeated 4 months later with 0.75 mg Cosyntropin, she had a clinical seizure without an EEG accompaniment 5 hours after injection, and a clinical and left temporal electrographic seizure 12 hours after injection. Serum cortisol had returned to normal (16.6 μg/dl) at the time of the seizure 5 hours after the second injection. It was not measured during the second seizure. She had had no seizures on Days −7 to −3, had two seizures on Day −2, one seizure on Day −1, and one seizure each on Days 2 and 3 ($P = 0.43$, by Poisson distribution, probability of seizures occurring after ACTH injection compared with average daily seizures for the week prior to ACTH). A third patient, a 30-year-old woman, experienced a flurry of seizures 3 to 4 days after injection, but this coincided with AED withdrawal as part of a presurgical evaluation.

In six of seven patients, no changes in EEG spikes were observed during the 24 hours following ACTH stimulation. The mean number of spikes during the 8-hour period from 8 AM to 4 PM was 54 per patient the day before ACTH injection, compared with 84 on the day of injection ($P = 0.7$). One patient had an increase in spike frequency 4 to 6 days after ACTH injection, coincident with AED withdrawal as part of a presurgical workup. One patient showed a spread in the spatial distribution of the interictal spikes during sleep (only) 15 to 22 hours after ACTH stimulation. She had left anterior temporal spikes limited to the sphenoidal and anterior temporal electrodes during the 3 days of monitoring before ACTH. After injection of 0.25 mg of Cosyntropin, the spikes involved the entire temporal area. This spatial spread was observed only during sleep the night after the injection, but not during wakefulness or during three preinjection and two further postinjection nights. When the injection was repeated with 0.75 mg Cosyntropin 4 months later, the peripheral field of the spikes included the lateral temporal area before ACTH injection, and no change was seen after injection.

Acute elevation of serum cortisol levels was observed in all patients, starting at 30 minutes after injection and returning to normal within 4 to 6 hours of injection (Table 2). The maximum serum cortisol elevation occurred 90 to 180 minutes after injection and ranged from 37 to 48 μg/dl. Acute elevation of ACTH was observed in all patients starting within 30 minutes of the injection, with return to baseline 1 to 3 hours after injection. The maximum elevation ranged from 37 to 81 IU (normal morning, 10–80 ng/L; evening, <50 ng/L). One of the patients whose serum progesterone levels were measured had an elevated serum progesterone level after injection, without EEG changes. Only minor elevations in serum DHEAS levels were seen in the three patients in whom these levels were measured, without associated EEG changes or seizures. None of the patients experienced any subjective stress or anxiety following the Cosyntropin injection. Two of seven patients felt mildly aroused for 2 to 3 hours after the injection.

4. Discussion

The present study illustrated that acute hypercortisolemia, produced as part of broad adrenal hormonal activation by ACTH stimulation to mimic the endocrine adrenal stress response, did not result in activation of interictal or ictal EEG activity in six of seven patients with stress-related LRE. Levels of cortisol reached in this study are comparable to those seen after physiological stress [4]. Despite the small number of patients, this pilot study suggests that hypercortisolemia of this degree, when occurring together with changes in other ACTH-stimulated adrenal hormones, is not a likely mechanism of acute stress-related seizure facilitation in patients with epilepsy.

In one patient, increased neuronal excitation more than 12 hours after ACTH injection was suggested by the spatial spread of the interictal spike field. However, this finding could not be reproduced when the testing was repeated several months later with a higher dose of ACTH and with the patients taking different AEDs.

Table 2
Serum cortisol levels (μg/dl)[a]

Patient	Sex	Age	−0.5 h	0 h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	4 h	5 h	6 h	7 h	8 h
1	F	30	16	22	28	36	38	39	38	38	—	20	—	8	—
2 0.25[b]	F	39	16	24	39	39	41	45	46	43	32	28	17	—	—
0.75[b]			10	—	26	—	31	33	35	38	26	**17**[c]	14	10	—
3	F	28	17		30	35	37	33	36	27	25	16	10	9	7
4	F	16	21	—	34	40	43	46	48	—	—	—	—	—	—
5	M	45	15	21	27	35	36	41	40	37	28	16	11	8	—
6	M	42	26	—	31	35	34	37	34	33	—	17	12	8	6
7	M	13	16	21	30	32	37	34	34	18	9	5	1	2	**3**[c]

[a] Serum cortisol drawn for up to 8 hours after ACTH injection.
[b] 0.25 and 0.75 Cosyntropin injection.
[c] Seizure occurred at this time.

The study has limitations. Subjects were identified as having stress-induced seizures by using a retrospective questionnaire, with the possibility of recall bias. Second, the number of patients studied is small, making this a very preliminary investigation.

The ACTH stimulation test used to induce hypercortisolemia in the present study is not a selective tool. The test stimulates secretion of all adrenal hormones. The adrenal gland secretes several steroids other than cortisol that have neuroactive properties, with both neuroexcitatory, proconvulsant and neuroinhibitory, anticonvulsant effects. The sulfated steroids pregnenolone sulfate and DHEAS exert a proconvulsant effect [5], whereas allopregnanolone and tetrahydrodeoxycorticosterone, the respective metabolites of progesterone and deoxycorticosterone, have potent anticonvulsant effects in animal models [6]. It is possible that stress response in patients with stress-sensitive seizures may favor unequal production of the excitatory and inhibitory neuroactive steroids and that it is the balance among all the steroids, as well as the effect of neuroactive stress-related peptides such as corticotropin-releasing factor, that determines the effect of stress on a given patient's seizures. An alternative hypothesis is that normal levels of adrenal hormones following stress elicit an abnormal excitatory neuronal response and facilitate seizures in some susceptible patients with epilepsy. Another possible explanation is that central mechanisms of stress response, including increased activity of stress-related peptides such as corticotropin-releasing factor or of stress-related neurotransmitters such as noradrenaline, rather than changes in peripheral hormonal secretion, may be involved. It is also possible that in some patients the feelings of stress experienced before a seizure could, in fact, represent the symptomatic beginning of the seizure rather than a trigger of the seizure.

A systematic study of the effects of individual neuroactive stress-related steroids, peptides, and neurotransmitters may help in understanding the role of hormones in stress-related modulation of seizures.

References

[1] Frucht MM, Quigg M, Schwaner C, et al. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 2000;41:1534–9.
[2] Klein P, Pezzullo JC. Effect of stress on localization-related epilepsy. Epilepsia 2000;41(Suppl. 7):112.
[3] Roberts AJ, Keith LD. Mineralocorticoid receptors mediate the enhancing effect of corticosterone on convulsion susceptibility in mice. J Pharmacol Exp Ther 1994;270:505–11.
[4] Spencer RL, Kalman BA, Dhabhar FS. Role of endogenous glucocorticoids in immune system function: regulation and counterregulation. In: McEwen BS, editor. Handbook of physiology, Sec. 7. vol. IV. Coping with the environment: neural and endocrine mechanisms, New York: Oxford University Press; 2001.
[5] Reddy DS, Kulkarni SK. Proconvulsant effects of neurosteroids pregnenolone sulfate and dehydroepiandrosterone sulfate in mice. Eur J Pharmacol 1998;345:55–9.
[6] Reddy DS, Tabatabai N, Rogawski MA. Stress-induced deoxycorticosterone-derived neurosteroids modulate GABAa receptor function and seizure susceptibility. J Neurosci 2002;22:3795–805.