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·Original Article·

Changes of serum adrenocorticotropic hormone and cortisol levels during sleep seizures

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Abstract: Objective Measuring the serum concentrations of adrenocorticotropic hormone (ACTH) and cortisol in epileptic seizures during sleep to investigate their link to the EEG changes. **Methods** Pre-surgical evaluation was performed by video-EEG monitoring using 24 channel recording. Thirty six epilepsy patients could be attributed to two groups: 28 patients had spontaneous seizures, and the other 8 patients whose seizures were induced by bemegride. Another 11 persons with confirmed psychogenic non-epileptic seizures (PNES) served as control group. Blood samples were obtained at five points: wake (08:00 a.m.), sleep (00:00 a.m.), and shortly before, during and after an epileptic seizure. The serum ACTH and cortisol were measured and analyzed by chemiluminescent immunoassay. **Results** The levels of ACTH and cortisol in serum underwent significant changes: declining below the average sleep-level shortly before seizures, increasing during seizures, and far above the average wake-level after seizures ($P < 0.001$). Such changes did not occur in the control group ($P > 0.05$). The ACTH and cortisol levels had no significant difference between spontaneous group and bemegride-induced group ($P > 0.05$). **Conclusion** The serum concentrations of ACTH and cortisol during sleep seizures are linked with pre-ictal and ictal EEG changes in epilepsy patients.

Keywords: seizures; sleep epilepsy; adrenocorticotropic hormone; cortisol; EEG

1 Introduction

Epileptic seizures are transient disturbances of cerebral function caused by sudden and abnormal neuronal discharges[1]. Adrenocorticotropic hormone (ACTH) and cortisol levels vary greatly between day and night. In an extensive review of the relationship between steroid hormones and excitability in the mammalian brain, Joels M discussed its consequences for long term potentiation and epilepsy[2]. In the present study, we further examined correlations between the ACTH and cortisol levels and the nocturnal seizures in human subjects with epilepsy.

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2 Materials and methods

2.1 Subjects Thirty six epilepsy patients who were being assessed for the neurosurgical treatment of their seizures at Shanxi Medical University participated in the present study. The average age of them was (21.14±6.90) years (ranging from 16 to 40 years), and the average duration of epilepsy was (3.25±0.98) years (ranging from 2 to 6 years). According to the classification of seizures proposed by the International League Against Epilepsy[3], the 36 cases could be divided into 2 groups: 28 patients had generalised seizures or partial seizures with secondary generalization, while the other 8 patients only had simple partial seizures. During the investigation, the 28 subjects had spontaneous seizures, and the seizures in the 8 subjects were induced by bemegride. Another 11 patients with confirmed psychogenic non-epileptic seizures (PNES) constituted a control group.

The extra procedures needed for this study and its reason had been explained to all subjects and the informed con-

sent was obtained from every participant. All patients had normal blood cell counts, hepatic and renal function; specific diabetes, pituitary pathology, rheumatoid arthritis and systemic lupus erythematosus had been excluded. The research protocol was in agreement with Chinese ethics supervision requirements.

2.2 Instruments and blood sampling A 24-channel video-EEG equipment (Nanjing Weisi Company, China) was used for monitoring seizures. Blood samples were collected to ethylene diamine tetra-acetic acid (EDTA) coated tubes from the indwelling catheters in the median cubital vein. Samples were taken at five time points: 1, wake (08:00 a.m.); 2, sleep (00:00 a.m.); 3, immediately before a noctural seizure (pre-seizure; aura of a seizure: like grunting or a simple shout, twitching of the lips or nasal alae or even the entire half of the face); 4, during the noctural seizure (during-seizure; EEG: bilaterally synchronous discharges); and 5, after the seizure (post-seizure; EEG: isoelectric activity). A neurologist, a clinical neurophysiologist and a nurse who took the blood-samples were present throughout the observation period.

Immediately after collection of the blood samples, serum was separated by a centrifuge at 2 500 r/min and refrigerated at -20 ºC. If seizures continued for more than 5 min, 10-20 mg diazepam was intravenously administered. Serum ACTH and cortisol levels were determined by chemiluminescent immunoassay. IMMULITE-ACTH and IMMULITE-Cortisol reagents were obtained from Diagnostic Products Co., USA.

In simple partial seizure patients, seizures were induced by intravenous administration of 25% bemegride at a rate of 10 mL/min (maximum 60 mL), guided by EEG and clinical observation. Verbal suggestion and intravenous administration of normal saline were used combinedly in PNES patients for induction of seizures[4].

2.3 Statistical analysis Data were measured repeatedly and analyzed by ANOVA using SPSS 11.5 software. $P < 0.05$ was considered statistically significant.

3 Results

3.1 ACTH in serum In the epilepsy patient group (n =36), the change of serum ACTH showed a course declining from wake status to sleep status, slightly falling just before a seizure, and then rising steeply during and after the seizure ($F = 20.925$, $P < 0.001$). The pre-seizure ACTH level was 2.9 times lower than the wake level and 1.4 times lower than the sleep level; the ACTH levels during and post-seizure were respectively 3.4 times and 8.5 times higher than the pre-seizure ACTH level (Tab. 1 and Fig. 1). There were 29 patients (80.6%) whose pre-seizure levels were lower than the lowest value of sleep status (00:00 a.m.), and 32 patients (88.9%) whose post-seizure ACTH levels surpassed the highest value of the wake status (08:00 a.m.).

In the PNES control group, the ACTH levels at wake status (08:00 a.m.) and sleep status (00:00 a.m.) had no significant changes compared with those in the epilepsy group; the ACTH levels of pre-, during, and post-seizure were similar to the wake status.

3.2 Cortisol in serum The average serum cortisol levels of the 36 epilepsy patients changed significantly among different time points ($F = 42.324$, $P < 0.001$). The pre-seizure cortisol level was respectively 2.27 times and 1.01 times lower than that at 08:00 a.m. and 00:00 a.m.; the levels during and post-seizure were respectively 2.44 times and 3.30 times higher than the pre-seizure level (Tab. 1 and Fig. 2). There were 26 patients (72.2%) whose pre-seizure cortisol levels declined toward the lower boundary of normal figures, and 22 patients (68.8%) whose post-seizure levels surpassed the maximum boundary of normal figures.

In the PNES group, the cortisol levels of pre-, during and post-seizure statuses were just slightly higher than that of wake status and negligible ($P > 0.05$).

3.3 Association of ACTH and cortisol levels with epileptic seizures Changes of ACTH and cortisol concentrations were associated with either spontaneous or bemegride-induced epileptic seizures, between which no significant differences were found (ACTH: $F = 0.194$, $P = 0.0663$; cortisol: $F = 0.000$, $P = 0.991$), suggesting that the effect of bemegride on ACTH and cortisol levels was not independent of seizure induction. (Tab. 2, Fig. 3)

3.4 EEG changes All the 36 cases exhibited pre-ictal EEG changes, started during sleep stages 1-2, on average 26 s before seizure (range 7-57 s). In 22 patients, the background rhythm did not change, but appeared a few spikes/sharp waves (3-4 Hz spike/sharp-slow waves) or many scattered sharp-slow waves; in 2 patients, the rhythmic spike/sharp waves appeared; in 4 patients, the background activity changed into low amplitude fast waves, then the frequency and amplitude increased and the clinical seizure started; in 6 patients, the background waves slowed down and the ampli-

tude went up from high amplitude θ waves to extremely high amplitude δ waves immediately before seizure; in 2 patients, the amplitudes of background waves suddenly declined before clinical seizure. During clinical seizures the EEG was difficult to assess because of the electromyographic and movement artefacts. The clinical seizures persisted for average 2.5 min after onset (ranging 2-5 min). After offset, the EEG showed isoelectric activity, for average 32 s (ranging 5-52 s).

No changes in background activity were observed before PNES. The EEG assessment during the PNES was as well

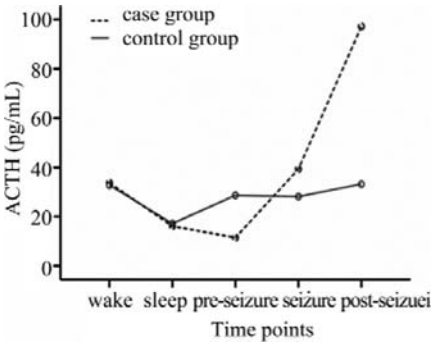

Fig. 1 Changes of ACTH level at different time points in case group and the control.

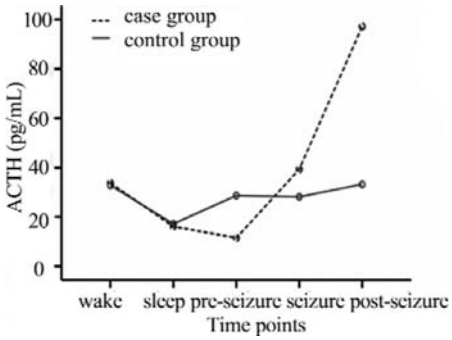

Fig. 2 Changes of cortisol level at different time points in case group and the control.

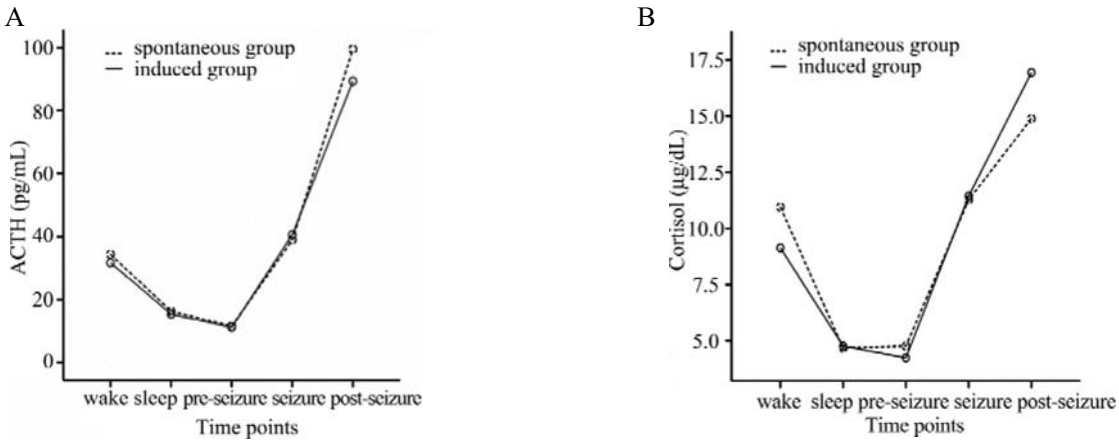

Fig. 3 ACTH (A) or cortisol (B) levels had no significant differences between spontaneous seizure and induced seizure. $P > 0.05$.

Tab. 1 Levels of ACTH and cortisol between case and control groups at different times (mean±SD)

Group	Number	Time point	ACTH (pg/mL)	Cortisol (μg/dL)
Case	36	wake	33.765±6.5940	10.550±2.4558
		sleep	16.133±3.2790	4.694±0.9171
		pre-seizure	11.486±5.1339	4.644±1.8709
		seizure	39.317±20.2941	11.311±4.9075
		post-seizure	97.217±59.0619	15.344±5.0124
Control	11	wake	32.790±6.5180	11.327±2.1467
		sleep	17.191±2.1533	4.791±0.7162
		pre-seizure	28.655±8.6097	12.836±5.3309
		seizure	28.136±8.7265	13.882±4.9207
		post-seizure	33.236±10.3051	13.536±5.7308

Tab. 2 Levels of ACTH and cortisol in spontaneous and induced groups at different times (mean±SD)

Group	Number	Time point	ACTH (pg/mL)	Cortisol (μg/dL)
Spontaneous	28	wake	34.340±4.8860	10.954±2.2252
seizure		sleep	16.336±3.2489	4.675±0.9466
		pre-seizure	11.579±5.3290	4.761±2.0058
		seizure	38.954±22.1519	11.275±4.9932
		post-seizure	99.479±60.6224	14.899±5.1059
Induced	8	wake	31.710±10.9180	9.138±2.8505
seizure		asleep	15.425±3.5192	4.763±0.8618
		pre-seizure	11.162±3.6812	4.238±1.3190
		seizure	40.588±12.8128	11.438±4.9219
		post-seizure	89.300±56.3398	16.938±4.6186

as impossible to obtain because of the electromyographic and movement artefacts.

4 Discussion

Our study intended to clarify the relationship between the hypothalamic-pituitary-adrenal axis and epileptic seizures during sleep. The control group was composed of patients with confirmed PNES, the onset of which were not accompanied by changes in ACTH levels[5]. Seizures during sleep most likely occur between 2-3 o'clock in the morning or about 30 min after falling asleep or 30 min before waking up. At these times ACTH and cortisol levels are usually at the lowest level of the day, which might trigger seizures in seizure-prone subjects.

In order to confirm this hypothesis we measured ACTH and cortisol levels at critical moments in epilepsy patients. Our results showed that at midnight during sleep both ACTH and cortisol levels were lower than those in the morning when patients were wake. However immediately before a seizure, the ACTH and cortisol levels were even lower than those at midnight; and during and after a seizure, the ACTH and cortisol levels increased even beyond daytime levels. In the PNES control group, ACTH and cortisol levels was also decrease during sleep; however, their during- and post-seizure levels were found no significant change compared with the corresponding pre-seizure levels despite clinical seizure-like movements. In persons with PNES, the pre-seizure level was closer to the wake level but not the sleep level, in accordance with the fact that PNES only occur when a trigger reaches the waking mind. The fact that PNES were also observed at night could be explained by pre-ictal pseudosleep[6]. Therefore the decrease of ACTH and cortisol levels may trigger/facilitate epileptic seizures, which then inversely stimulate an increase of ACTH and cortisol beyond wake level, but not increase muscular activity since this increase is absent in the PNES. A possible explanation for the observed phenomenon may be that the nocturnal ACTH levels decrease to a threshold triggering the release of corticotropin-releasing hormone (CRH), which in turn lower the threshold of seizure activity[7].

No matter which kind of the epileptic seizure, spontaneous or bemegride induced, the changes in ACTH and cortisol levels were the same, hence the question whether bemegride has an independent effect on ACTH and cortisol release. There were two patients whose ACTH and cortisol levels did not change after administrated with the highest admissible dose of bemegride, the highest admissible dose of bemegride did cause changes in the EEG, but did not provoke clinical seizures. It has been known that seizures are associated with changes in hormone levels[8,9], but its exact relationship to electroclinical events was obscure.

The present study is hardly to assess the causality between pre-ictal neuronal activity and ACTH: whether the pre-ictal neuronal activities stimulate the CRH release and cause the seizure or the gradually decreased ACTH levels during the night trigger the CRH release and induce the pre-ictal and ictal neuronal activities. We hypothesized that the low ACTH level induced CRH release triggered seizures; while the seizures may be responsible for the subsequent increase of pituitary-adrenal hormone levels, because ACTH and cortisol rose to high levels during seizures and reached their highest levels after seizures.

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睡眠癫痫发作时血清促肾上腺皮质激素和皮质醇的变化

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摘要：目的 探讨睡眠癫痫患者临床发作时血清促肾上腺皮质激素（adrenocorticotropic hormone，ACTH）和皮质醇的变化及其与脑电波变化之间的联系。**方法** 采用24导video-EEG对睡眠癫痫患者进行脑电监测，并对其发作前瞬时的EEG进行分析，采用化学发光免疫法在清醒时、睡眠时、发作前瞬间、发作时和发作后的5个时间点测定血清中ACTH和皮质醇的浓度。在36例睡眠癫痫患者中，28例为自然发作，8例为贝美格诱发发作。用11例假性心因性癫痫发作患者作为对照组。**结果** 睡眠癫痫发作前、中、后血清ACTH和皮质醇的浓度有显著差异（$P < 0.001$），发作前瞬间降低，发作时升高，发作后明显升高；假性癫痫发作对照组的血清ACTH和皮质醇浓度在发作时无明显变化（$P > 0.05$）；贝美格诱发发作组与自然发作组间ACTH和皮质醇比较无显著差异（$P > 0.05$）。**结论** 睡眠癫痫患者血清ACTH和皮质醇与癫痫发作前和发作时的脑电变化有密切关系。

关键词：癫痫发作；睡眠癫痫；促肾上腺皮质激素；皮质醇；脑电波