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Original article

Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome

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Abstract

Purpose: To investigate whether serial electroencephalographic (EEG) findings can predict relapse of epileptic spasms after synthetic adrenocorticotropic hormone (ACTH) therapy in patients with West syndrome (WS).

Subjects and methods: Thirty-nine WS patients (8 cryptogenic and 31 symptomatic) were included in this study. These patients received ACTH therapy for the first time and were regularly followed up for more than three years at our hospital. Sixteen patients (41.0%) showed seizure relapse (relapse group) and 23 patients (59.0%) did not show relapse (non-relapse group). We used survival analysis to investigate the influence of etiology and presence of epileptic discharges after the ACTH therapy on seizure outcome.

Results: Immediately after the ACTH therapy, etiology was associated with seizure outcome ($p = 0.003$). In the early stage (1 month after the ACTH therapy), only the presence of epileptic discharges ($p = 0.001$) had a significant association with seizure outcome, regardless of etiology. Because all relapsed patients were in the symptomatic group, we performed the same statistical analysis on symptomatic WS patient data only. We found that the group with no epileptic discharges on EEG showed a significantly higher seizure-free rate than those with epileptic discharges in the early stage ($p = 0.0091$).

Conclusion: This study demonstrated that serial EEG findings after ACTH therapy are significantly related to relapse of epileptic spasms.

Keywords: EEG; ACTH therapy; West syndrome; Seizure outcome; Epileptic discharges; Prediction of seizure relapse

1. Introduction

West syndrome (WS) is an age-dependent epileptic encephalopathy that causes psychomotor deterioration even in normally-developed infants. Mental outcome is particularly poor in patients whose epileptic spasms (infantile spasms) cannot be controlled by treatment. Adrenocorticotropic hormone (ACTH) therapy is considered the most effective therapy for WS, and its initial effect is reported to be excellent [1–13]. However, nearly one-half of patients whose spasms were once suppressed experience relapse [1,5,14–16]. Despite the fact that relapse after ACTH therapy is such a relevant issue, the factors related to relapse and its prevention have not yet been fully investigated. Because electroencephalography

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(EEG) precisely reflects epileptic brain dysfunction in WS patients, we suggest that it could be a powerful tool for treatment of patients with WS. Although there are several studies on EEG changes during and after ACTH therapy [17–19], there are few detailed studies on the relationship between EEG features after ACTH therapy and relapse of epileptic spasms.

In this study, we investigated predictive factors for relapse of epileptic spasms after ACTH therapy in patients with WS, focusing especially on the issue of whether serial EEG findings can predict relapse.

2. Subjects and methods

2.1. Patients and ACTH therapy protocol

Sixty-six WS patients were admitted to the Department of Child Neurology in Okayama University Hospital between January 2000 and August 2010 and received synthetic ACTH therapy. All patients had spasms and hypsarrhythmia on EEG. Among these patients, those who fulfilled all of the following criteria were included in this study: (1) received their first ACTH therapy; (2) showed spasm cessation and hypsarrhythmic EEG pattern disappearance upon completion of ACTH therapy; (3) completed ACTH therapy according to the Okayama University Hospital protocol; and (4) were regularly followed-up after completion of ACTH therapy with detailed clinical observation and EEGs for more than three years. According to the International Classification of Epilepsies and Epileptic Syndromes (ILAE, 1989), patients with underlying known etiology or previous signs of brain damage (psychomotor retardation, neurological signs, radiological signs or other types of seizures besides spasms) were categorized into the symptomatic group. The cryptogenic group was characterized by a lack of previous signs of brain damage and known etiology [20].

According to the Okayama University Hospital ACTH therapy protocol, synthetic ACTH was administered intramuscularly once daily at a dose of 0.005–0.015 mg (0.2–0.6 IU)/kg/day for 14 consecutive days. If spasms or epileptic discharges on EEG remained, the same or an increased ACTH dose (0.005–0.025 mg/kg/day) was continued, and ACTH therapy was stopped when the effect of ACTH for each patient reached a plateau. ACTH was administered for up to 35 days.

2.2. EEG and etiology analysis

After completing ACTH therapy, all patients underwent repeated EEG recordings every two to four weeks. These serial EEGs were classified into five stages according to the timing after the end of ACTH therapy: immediate stage (immediately after); very early stage (2 weeks after); early stage (1 month after); and middle stage (3 months after). We selected and analyzed EEGs that were recorded on the day nearest to the timing of each stage. We also defined late stage EEG as the first EEG recorded after four months for each patient. EEGs were recorded for more than 40 min, while the patient was both asleep and awake, using a Nihon Kohden Neurofax or NEC SINAFIT 1000.

Two pediatric neurologists (Y.H. and H.Y.) independently evaluated the EEGs. If there was any disagreement regarding EEG findings, including the definition of hypsarrhythmia, a final decision was reached through advice given by a third pediatric neurologist (Y.O.) who was blinded to information related to the patients' clinical background. We used survival analysis to investigate the influence of etiology (cryptogenic or symptomatic) and the presence of epileptic discharges after completion of ACTH therapy on seizure outcome. Kaplan–Meier analysis, the log-rank test and the Cox proportional hazards model were used for statistical analysis. Differences were considered to be significant with p values less than 0.05.

We also analyzed the changing course of epileptic discharges over time in the group of patients with no relapse of spasms (non-relapse group) and the group of patients with relapse of spasms (relapse group). This analysis focused on how spikes developed into hypsarrhythmia in the relapse group after completion of ACTH.

2.3. Medical treatment after completion of ACTH therapy

If an antiepileptic drug (AED) was partially effective before ACTH therapy or if it was continuously administered during ACTH therapy, the same AED was generally used after ACTH therapy. Otherwise, we chose valproic acid (VPA), which was reported to show relatively high efficacy [13,21,22] and rapid appearance of effect, to allow efficacy to be determined in a short period of time. VPA was administered to 27 patients, zonisamide to 13 patients, clonazepam to 10 patients and other AEDs to 7 patients. All patients were hospitalized until at least two weeks after completion of ACTH therapy, and they were treated as outpatients every two to four weeks after discharge.

3. Results

3.1. Patient characteristics

Of the 66 patients with WS who were treated at our hospital, 39 patients (24 boys and 15 girls) were analyzed in this study. The remaining 27 patients were excluded for the following reasons: 6 patients were receiving ACTH therapy for the second time; 1 patient