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

Yumiko Hayashi¹, Harumi Yoshinaga¹, Tomoyuki Akiyama², Fumika Endoh², Yoko Ohtsuka¹,³, Katsuhiro Kobayashi²

¹Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
²Department of Child Neurology, Okayama University Hospital, Okayama, Japan
³Current affiliation: Asahigawaso Rehabilitation and Medical Center, Okayama, Japan

Corresponding author: Yumiko Hayashi, MD
Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
2-5-1 Shikata-cho, Kita-ku, Okayama, 700-8558, Japan
Telephone number: +81-86-235-7372
Fax number: +81-86-235-7377
E-mail address: gmd19010@s.okayama-u.ac.jp

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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 (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 [17,18,19], 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.

1. Subjects and methods

1.1. 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 to 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.

### 1.2. 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.

1.3.  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.

2. Results

2.1. 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 received steroid pulse therapy for a lung disease before ACTH therapy; 12 patients showed no suppression of spasms by ACTH therapy; 6 patients had ACTH therapy discontinued because of worsening spasms and/or EEG findings or infection; and 2 patients were lost to follow-up. Eight patients (20.5%) were classified as having cryptogenic WS and 31 patients (79.5%) were classified as having symptomatic WS. The total duration of ACTH therapy ranged from 11 to 37 days (mean: 23.5 days). Additional ACTH therapy was performed in 38 out of the 39 patients. Ten patients (5 in the non-relapse group and 5 in the relapse group) received additional therapy because of the persistence of epileptic spasms, and 28 patients (17 in the non-relapse group and 11 in the relapse group) received additional therapy because of spikes on EEG at 14 days after the start of ACTH therapy. The age at onset of spasms ranged from 2 to 15 months (mean: 6.7 months). The follow-up period ranged from 3 years, 0 months to 12 years, 9 months (mean: 7 years, 5 months). Sixteen patients (41.0%) had seizure relapse after ACTH therapy (relapse group) with epileptic spasms, and all of them belonged to the symptomatic group.

No relapse was observed in 23 patients (59.0%) (non-relapse group: 15 symptomatic and 8 cryptogenic
patients). Table 1 shows the characteristics of symptomatic patients. In patients with symptomatic WS, the etiology was not different between the non-relapse and the relapse groups (Table 1). The length of time from the end of ACTH therapy to seizure relapse was 5 days to 25 months (mean: 6.6 months). Only three patients relapsed between five days and one month after completion of ACTH therapy, and the remaining patients relapsed at two months or thereafter.

2.2. Association between EEG findings and relapse

EEGs in the immediate stage were recorded on - 0.18 ± 1.10 days (mean ± standard deviation [SD]), those in the very early stage on 12.18 ± 2.27 days, those in the early stage on 30.64 ± 5.97 days and those in the middle stage on 90.64 ± 14.02 days. The late-stage EEGs were recorded on 146.51 ± 19.06 days.

We compared EEG findings between the relapse and the non-relapse groups at each stage after completion of ACTH therapy (Figure 1). In the immediate stage, the existence rate of epileptic discharges did not differ between the non-relapse group and the relapse group. In the very early stage, spikes were observed in 16 patients (69.6%; 5 cryptogenic patients and 11 symptomatic patients) in the non-relapse group, and in 16 patients (100%) in the relapse group. After the reappearance of spikes on EEG in the very early stage, epileptic discharges did not disappear in any patient in the relapse group until the seizures returned. However, in all patients except for one symptomatic patient in the non-relapse group, the epileptic discharges disappeared at least once by the middle stage. The appearance rate of epileptic discharges decreased gradually towards the middle stage in the non-relapse group.

The locations of epileptic discharges in the immediate stage did not differ between the non-relapse and
relapse groups. In the non-relapse group, the number of patients with multifocal spikes decreased along with the decrease in the number of patients with spikes until the middle stage. In the relapse group, “multifocal” cases (including hypsarrhythmia) subsequently increased, and all patients showed “occipital” or “multifocal” spikes after the middle stage. Hypsarrhythmia reappeared in the early stage in one patient, in the middle stage in three patients and in the late stage in six patients. Seven patients developed spasms without recurrence of hypsarrhythmia on EEG (Table 1). Representative EEG changes in one patient each in the relapse and non-relapse groups are shown in Figure 2.

### 2.3. Association of relapse with EEG findings and etiology

Figure 3 shows Kaplan-Meier curves of the seizure-free rate over time in the group with no epileptic discharges and in that with epileptic discharges on EEG performed in the immediate, very early and early stages. Most relapses occurred in the middle stage and thereafter. Therefore, we chose EEGs in the above-mentioned three stages for relapse prediction analysis. Overall, the group with no epileptic discharges on EEG in the very early stage ($p = 0.04$) and the early stage ($p < 0.001$) showed a significantly higher seizure-free rate, whereas there was no significant difference in the seizure-free rate between the two groups in the immediate stage ($p = 0.3326$).

Because all relapsed patients were in the symptomatic group, we performed statistical analysis on data from symptomatic patients only to avoid any selection bias. Patients without epileptic discharges on EEG in the early stage showed a significantly higher seizure-free rate than those with epileptic discharges ($p = 0.0091$). Also, patients without epileptic discharges in the very early stage showed a lower seizure relapse
rate than those with epileptic discharges on EEG in that stage, though it did not reach the statistical

significance \((p = 0.0729)\). In contrast, there was no significant difference in the seizure-free rate between the

patients with epileptic discharges and those without epileptic discharges on EEG in the immediate stage \((p =

0.8162; \text{Figure 4}).

We also performed multivariate analysis using the Cox proportional hazards model, and included
etiology as a covariable in addition to epileptic discharges. In the immediate stage, the presence of epileptic

discharges on EEG had no influence on the seizure-free rate; however, etiology had an influence \((p = 0.003),

with symptomatic patients having a lower seizure-free rate than cryptogenic patients. In the very early stage,

the presence of epileptic discharges \((p = 0.02)\) and etiology \((p = 0.009)\) significantly affected the seizure-free

rate. Patients with epileptic discharges and those with symptomatic etiology had a lower seizure-free rate. In

contrast, in the early stage, only the presence of epileptic discharges was associated with seizure relapse \((p =

0.001), \text{regardless of etiology.}

3. Discussion

Regarding the relapse of spasms after ACTH therapy, Ohtsuka et al. reported that seizures relapsed in 10%
of cryptogenic WS patients and in 49.3% of symptomatic WS patients in long-term follow-up [1]. Other

investigators also reported that 14.3 to 46.2% of cryptogenic WS patients and 21.7 to 47.4% of symptomatic

WS patients had seizure relapse after initial therapy, including ACTH therapy [5,14-16,23,24]. In the present

study, there was no seizure recurrence in the cryptogenic patients and in 51.6% of the symptomatic patients.

Although relapse after ACTH therapy is both a relevant and important issue, there are few detailed studies
on the relationship between seizure relapse and EEG findings in patients with WS. This might be because

the usefulness of a detailed analysis of follow-up EEGs after completion of ACTH therapy has not been

widely recognized.

Itomi et al. concluded that the existence of focal EEG abnormalities (spikes, sharp waves and

high-voltage slow waves) was not related to the seizure outcome three months after starting the initial

therapy [3], suggesting that EEG abnormalities are not useful in predicting seizure outcome after various

therapies, including ACTH. However, after reviewing their data thoroughly, we found that all patients whose

EEG abnormalities resolved by three months after treatment had no recurrence of spasms before the end of

follow-up. Recently, Yamada et al. concluded that disappearance of epileptic activity might be associated

with a sustained response without relapse after initial treatment (high-dose vitamin B6, zonisamide, sodium

valproate and ACTH) [19]. Gaily et al. reported that persistent multifocal spikes were always associated

with continuing spasms after vigabatrin therapy [4]. Koo et al. reported that persistence of hypsarrhythmia

or failure of EEG normalization for two weeks or more after initiation of ACTH therapy correlated with

poor cognitive outcome [5].

The present study is the first to statistically indicate that the appearance of epileptic discharges after

completion of ACTH therapy was related to seizure outcome. Overall, including both cryptogenic and

symptomatic patients, the group with no epileptic discharges on EEG at approximately two weeks and at one

month after the end of ACTH therapy showed a significantly higher seizure-free rate. Results of the second

analysis, which excluded the cryptogenic patients, were almost the same: the group with no epileptic

discharges on EEG at approximately one month after completion of ACTH therapy showed a significantly
higher seizure-free rate.

In our study, the time to relapse after completion of ACTH therapy ranged from 5 days to 25 months (mean: 6.6 months). Riikonen reported that seizure relapse occurred a few days to 18 months (mean: 4.6 months) after completion of ACTH therapy [17], and Lin et al. reported that relapse occurred 4.6 ± 1.8 months after completion of ACTH therapy [6]. Our data were compatible with those of these previous studies and most patients relapsed two months or later after completion of ACTH therapy. Therefore, the presence of epileptic discharges, especially multifocal spikes before two months, can be used as a warning sign of imminent relapse. In addition, our study indicated that once epileptic discharges disappeared during this period, the possibility of spasm relapse would be reduced even though epileptic discharges later reappeared.

Multivariate analysis on the entire study population showed that etiology was another significant predictive factor for relapse. It was the only significant predictive factor for relapse immediately after ACTH therapy. At approximately two weeks after completion of ACTH therapy, the presence of epileptic discharges on EEG also becomes a significant predictive factor, together with etiology. At one month after completion of ACTH therapy, the presence of epileptic discharges becomes the only significant predictive factor. These findings suggest that both cerebral dysfunction caused by organic brain damage and epileptogenesis expressed as epileptic discharges are complicedly associated with seizure relapse after ACTH therapy. The results of the present study indicate that detailed EEG investigation after ACTH therapy, particularly in symptomatic patients, can be a useful tool for predicting seizure relapse.

The universal guidelines for treatment after ACTH therapy have not yet been established. In our
hospital, we perform AED treatment after ACTH therapy for all patients, although AED treatment after
ACTH therapy varies from place to place, including no AED treatment for patients without clinical seizures
and prolonged intermittent use of ACTH for patients who experience relapse [25]. Once WS occurs or
relapses, the efficacy of conventional AEDs decreases [27-29]. Yoshinaga et al. proposed early AED
intervention before the onset of WS for high-risk patients based on the experience of successfully treating
some patients [26]. Early intervention or enhancement of AED treatments using EEGs after ACTH therapy
might also be promising to prevent relapse of spasms. Although, we usually use VPA after ACTH therapy
because of its high and rapid efficacy [16,26], other AEDs, such as zonisamide, topiramate, lamotrigine and
levetiracetam, might be more beneficial [11,23,30]. EEG-based intensive AED treatment to prevent relapse
of spasms after ACTH therapy should be administered for a maximum of approximately 2 years to avoid
unnecessary long-term treatment, because relapse of spasms occurred by 25 months after completion of
ACTH therapy in the present study.

A limitation of this study is that it was not strictly designed prospective study. Despite this limitation,
we obtained some significant findings. Larger-scale prospective studies are needed to confirm these results
as well as the significance of prophylactic therapy to prevent relapse of spasms after ACTH therapy.

In conclusion, we recommend regular follow-up examinations for the first two months after
completion of ACTH therapy, including detailed EEGs, in WS patients especially symptomatic patients.
During this time, the persistence or worsening of epileptic discharges on EEG, especially multifocal epileptic
discharges, is highly predictive for imminent relapse of spasms.
Disclosures or conflict of interest

None of the authors has any conflict of interest to disclose.

References


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BM, brain malformation; IH, intracranial hemorrhage; PI, premature infant; MC, multiple conception; HIE, hypoxic-ischemic encephalopathy; TS, tuberous sclerosis; M, month(s); N/A, not applicable

No. 9-23 are in the non-relapse group; No. 24-39 are in the relapse group
Figure legends

Figure 1. Location of epileptic discharges after completion of ACTH therapy

The number in parentheses is the number of patients. We classified the distribution of epileptic discharges on EEG after ACTH therapy as follows: “multifocal” (three or more independent foci), “occipital” (one focus or two independent foci limited to the parietal, post-temporal and occipital head areas) and “non-occipital” (one or two independent foci limited to the frontal, central, anterior temporal and midtemporal head areas).

() Number of cryptogenic patients * Number of patients with hypsarrhythmia

Figure 2. EEGs of a non-relapse patient and a relapse patient (sleep records)

(A) Immediate stage, (B) Very early stage (C) Early stage, (D) Middle stage

Non-relapse patient: (A) The epileptic discharges remained at the right parietal-posterior temporal-occipital head area and left frontal head area. (B) The epileptic discharges were observed in the right parietal and right frontal head areas. In addition to the spikes shown in this Figure, epileptic discharges in other areas, such as in the right posterior temporal-occipital and left frontal-anterior temporal head areas, were also observed. (C) and (D) All epileptic discharges disappeared.

Relapse patient: (A) The epileptic discharges were suppressed completely. (B) The epileptic discharges reappeared in the right occipital and left parietal head areas. In addition to these areas, epileptic discharges in other areas, such as in the left posterior temporal-occipital, bilateral midtemporal and right frontal head areas, were observed. (C) The epileptic discharges appeared in the left parietal and right frontal pole areas. We also observed multifocal epileptic discharges in the right parietal-occipital and right midtemporal head areas in
the same EEG recording. (D) Hypsarrhythmia evolved again.

Figure 3. Overall comparison of seizure-free rate between the group with spikes and the group without spikes

Black line: Patients with epileptic discharges. Dash line: Patients without epileptic discharges.

EEG results for the group with no epileptic discharges at the very early stage and the early stage showed a significantly higher seizure-free rate, whereas there was no significant difference in the seizure-free rate between the two groups at the immediate stage. * $p = 0.04$, ** $p < 0.001$

Figure 4. Comparison of seizure-free rate between the group with spikes and the group without spikes in symptomatic patients

Black line: Patients with epileptic discharges. Dash line: Patients without epileptic discharges.

The group with no epileptic discharges on EEG in the early stage showed a significantly higher seizure-free rate, whereas there was no significant difference in the seizure-free rate between the two groups in the immediate stage and the very early stage. * $p = 0.0091$