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Original article

Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders

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Abstract

To elucidate an effective therapeutic strategy for 'ESES syndrome', epilepsy with electrical status epilepticus during slow sleep (ESES) and its related epileptic disorders, we studied the effect of treatment on the EEG pattern of continuous spike-waves during slow wave sleep (CSWS) in 15 afflicted patients. Basically performed in the following order, the employed therapies included (1) high-dose valproate (VPA) therapy (serum level >100 μg/ml); (2) a combination therapy of VPA and ethosuximide (ESM); (3) short cycles of high-dose diazepam (oral or intrarectal DZP, 0.5–1 mg/kg per day for 6–7 days); and (4) intramuscular synthetic ACTH-Z therapy (0.01–0.04 mg/kg per day for 11–43 days). Regarding the initial EEG effect, a remission of CSWS was achieved by high-dose VPA therapy in 7 of 15 trials (47%), by the combination therapy of VPA and ESM in 3/7 trials (43%), by short cycles of high-dose DZP in 2/4 trials (50%), and by ACTH-Z therapy in 2/5 trials (40%). A permanent remission of ESES syndrome was achieved by high-dose VPA therapy and/or combination therapy of VPA and ESM in 10 patients (67%). The effects of short cycles of high-dose DZP and ACTH-Z therapy were at best temporary. Our strategy for the treatment of ESES syndrome is therefore considered valid.

Keywords: ESES; CSWS; High-dose valproate; Ethosuximide; Short cycle of high-dose diazepam; ACTH

1. Introduction

Epilepsy with electrical status epilepticus during slow sleep (ESES) is a serious disorder in childhood, with its extraordinary EEG abnormality of continuous spike-waves during slow wave sleep (CSWS) causing neuropsychological regression [1–4]. Although seizures and CSWS on EEG are age dependent and self-limiting, CSWS is often very intractable before adolescence, and the urgent suppression of this EEG abnormality is necessary to prevent the progression of neuropsychological impairment.

Over the years, besides typical ESES, several related epileptic disorders have been reported. Tassinari et al. [3] proposed the term 'encephalopathies with ESES (ESES syndrome)' to collectively indicate these disorders. We also reported that these disorders constitute a spectrum, sharing common clinical and EEG findings [5,6]. We have adopted the term 'ESES syndrome', which includes the following three different categories based on EEG patterns, seizure types, and neuropsychological findings: ESES; atypical benign partial epilepsy of childhood (ABPE), described by Aicardi and Chevrie [7]; and Landau–Kleffner syndrome (LKS).

In ESES, mental deterioration is noted in association with CSWS on EEG and may remain even after the improvement of EEG abnormality. In this category, a spike-wave index (percentage of time occupied by diffuse spike-wave activity on EEG) during slow-wave sleep is generally very high, and its subset group of patients show epileptic negative myoclonus [3,6,8]. ABPE shows atonic

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and absence seizures in association with CSWS on EEG, temporarily appearing during the clinical course of benign childhood epilepsy with centrotemporal spikes. It does not cause neurological regression [7]. LKS is an acquired epileptic aphasia that is often associated with CSWS on EEG.

A basic pathophysiology of ESES syndrome is supposed as CSWS on EEG or the 'electrical status' [3], and therefore treatment for ESES syndrome should be focused on the remission of CSWS. We have been treating many patients suffering from ESES syndrome, and in the present study we evaluated the efficacy of our treatment to suppress the EEG pattern of CSWS in order to establish the most adequate therapeutic strategy for ESES syndrome.

2. Patients and methods

The subjects of this study were 15 patients (8 males and 7 females) suffering from ESES syndrome with a spike-wave index during slow-wave sleep of at least 60%, and they were admitted to the Okayama University Hospital from 1985 to 2000. The follow-up period ranged from 2 years 2 months to exactly 18 years (mean: 10 years 11 months). The ages at the last follow-up ranged from 4 years 11 months to 24 years 8 months (mean: 16 years 4 months). These subjects included 13 patients with ESES, 1 with ABPE, and 1 with LKS.

They were treated with one or more of the following therapies: (1) a high-dose valproate (VPA) therapy [9], (2) a combination therapy of VPA and ethosuximide (ESM) [10], (3) short cycles of high-dose diazepam (DZP) [11], and (4) synthetic ACTH-Z (tetracosactide Zn) therapy.

Our basic therapeutic strategy was as follows. First, we started treatment with the VPA monotherapy, and unless there was a negative side effect, the dosage of VPA was increased every several days until the serum level was above 100 μg/ml. The serum levels of antiepileptic drugs were measured about 2 h after the morning administration. When the high-dose VPA therapy did not exert a satisfactory effect or the dose of VPA could not be increased because of negative side effects, we tried the combination therapy of VPA and ESM. When these two therapies were ineffective, we tried a short cycle of DZP therapy (0.5–1 mg/kg per day of oral or intrarectal DZP administration before the night's sleep) for 6–7 days. Ultimately 0.01–0.04 mg/kg per day of synthetic ACTH-Z was intramuscularly injected. During the period of high-dose DZP or ACTH-Z therapy, other treatment was continued.

Regarding the initial effect of the therapeutic trial, the therapy was judged effective when diffuse spike-waves disappeared or CSWS markedly dissipated on EEG (a decrease of spike-wave index to less than half of that before the introduction of treatment) for more than a month. A relapse of CSWS on EEG was defined as a reincrease of the spike-wave index to half or more of what it was before therapy. When a patient was more than 10 years old without any relapse of CSWS on EEG for more than a year, he or she was assumed to have attained a remission at the age of the improvement of CSWS. The relationship between the effect of each therapy and the following factors was statistically evaluated by using *t*-test or Fisher's exact test: presence or absence of an intracranial lesion, age at the initial observation of the EEG pattern of CSWS (which was assumed to be the age at the onset of ESES syndrome), and spike-wave indices (Table 1). In this study, the limit of statistical significance was $P=0.05$.

The spike-wave index was examined by recording overnight polysomnography, including scalp EEG, submental EMG, electrocardiography, electro-oculography, and respiratory movements of the thorax in 12 patients, by recording polysomnography of the first non-REM sleep cycle in another patient, and by nap EEG in the remaining 2. The MRI was examined in all patients.

3. Results

3.1. Efficacy of the therapy

3.1.1. High-dose VPA therapy (Tables 1 and 2)

The high-dose VPA monotherapy was tried once on all 15 patients. This therapy was effective in 7 (47%) of 15 trials, and CSWS disappeared on EEG without any relapse in all effective cases. There was no significant statistical difference in ages at the onset of ESES syndrome, the presence or absence of an intracranial brain lesion, spike-wave indices, or serum VPA levels between the responders and the nonresponders (Table 2).

3.1.2. The combination therapy of VPA and ESM (Tables 1 and 2)

The combination therapy of VPA and ESM was tried once in seven patients and was effective in 3 (43%). Up to the time of the last follow-up, none of the patients who responded to this therapy experienced any relapse of CSWS. The three effective cases were in the 6 patients who had been treated without success with the high-dose VPA therapy. Between the responders and the nonresponders, no difference in the serum levels of ESM and VPA was found. Other factors were not related to the efficacy of this therapy.

3.1.3. Short cycles of high-dose DZP (Tables 1 and 3)

The short cycle of high-dose DZP was tried once in four patients for whom the above-mentioned therapies had failed. It resulted in the initial efficacy in 2 (50%) of the 4, although a relapse of CSWS on EEG occurred in both of them. The duration of this therapy was 6 or 7 days. The total dose of DZP was 6.5 and 7.0 mg/kg (mean: 6.75 mg/kg) in the responders and 3.54 and 3.78 mg/kg (mean 3.66 mg/kg) in the nonresponders ($P=0.008$ by *t*-test) (Table 3)