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Original Article

Early diagnosis, treatment and prognosis of epilepsy with continuous spikes and waves during slow sleep

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Abstract: The study is to investigate the importance of early diagnosis and treatment to the prognosis of epilepsy with continuous spikes and waves during slow sleep (CSWS). A total of 8 cases of CSWS children were followed up for 6 months to 4 years. Retrospective analysis of the clinical and electroencephalographic (EEG) characteristics, treatment and prognosis was performed in these 8 cases. Of the 8 cases of CSWS patients, 5 were males and 3 were females. Epilepsy onset ages were from 3 years and 1 month to 10 years and 6 months. Five cases of the patients were with brain lesions while the other 3 cases appeared normally by imaging detection. After treatment with valproic acid, clonazepam, lamotrigine and hormone for 3 months, clinical symptoms and EEG were improved significantly in 7 cases. Two cases relapsed at 6 months after comprehensive treatment. For atypical early performance of CSWS, early diagnosis and regular treatment could improve the condition of children with seizures and effectively inhibit the epileptic activity with good prognosis.

Keywords: Epilepsy with continuous spikes and waves during slow sleep, electroencephalogram, clinical, treatment, prognosis

Introduction

Epilepsy with continuous spikes and waves during slow sleep (CSWS) is a rare neurological disease. CSWS is not an independent epilepsy syndrome but often accompanied by comprehensive damage of brain function and associated with various forms of epilepsy and neurodevelopmental problems. It is an epileptic syndrome which occurs in childhood period and seriously affects the cognitive function of children in childhood period [1]. Epileptic seizure, different degree of comprehensive brain dysfunction and electrical status epilepticus during slow sleep (ESES) are the main manifestations of CSWS. The incidence of CSWS accounts for 0.2% to 0.5% of childhood epilepsy. And, because of rareness, it is often not easy to identify, thus resulting in delay of treatment. It is reported that early diagnosis, effective treatment and termination of sustained spike wave discharge can improve the prognosis of patients with CSWS [2]. We retrospectively analyzed 8 patients with confirmed CSWS, hoping to deepen the understanding and improve the diagnosis, treatment and prognosis of CSWS.

Materials and methods

General clinical data

A total of 8 patients enrolled in this study were hospitalized in our department from January 2000 to December 2010. Detailed information of family history, past medical history, history of the present illness, neurological examination records and cranial CT and magnetic resonance imaging (MRI) examination results were available. Their clinical data were shown in **Table 1**. Among them, 5 patients were male and 3 patients were female. Their ages ranged from 3 years and 1 month to 10 years and 6 months, with the mean age of 5 years and 2 months. They were all diagnosed as CSWS and the duration was 4 months to 10 years. The clinical manifestation of the 8 cases all were epileptic seizures. Among them, one side limb clinic accompanied with typical absence seizures appeared in 1 case. Atypical absence and myoclonic atonic seizures lead to fall were observed in 5 cases. One case was observed with convulsions associated with absence seizures and 1 case with tonic clonic seizure. The daily epi-

Table 1. General clinical data

	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6	Case #7	Case #8
Gender	Male	Male	Female	Female	Male	Male	Female	Male
Onset age	3 years and 1 months	4 years and 5 months	5 years and 3 months	3 years and 8 months	4 years and 9 months	5 years and 1 months	4 years and 10 months	4 years and 11 months
Duration of disease	6 years	2 years	11 months	2 years and 6 months	1 year and 8 months	2 years and 3 months	10 months	1 year and 6 months
Perinatal period	Suspicious hypoxic history	_	_	_	Suspicious hypoxic history	Suspicious hypoxic history	Suspicious hypoxic history	Suspicious hypoxic history
Development before onset	Normal	Lag behind	Normal	Lag behind	Lag behind	Lag behind	Lag behind	Lag behind
Family history of seizures	+	_	+	+	+	+	+	_
Type of epileptic attack	A + B + C	A + B + C + drop attack	A + B + C	A + C + drop attack	A + drop attack + complex partial seizures	A + C	A + C+ complex partial seizures	A + B + C
Frequency of seizure	5-10+	10-20+	1-6	10-20+	1/week-1/month	3-9	10-11	1/week-1/month

Note: A: partial seizure generalization in sleep; B: partial motor seizures during wakefulness; C: atypical absences.

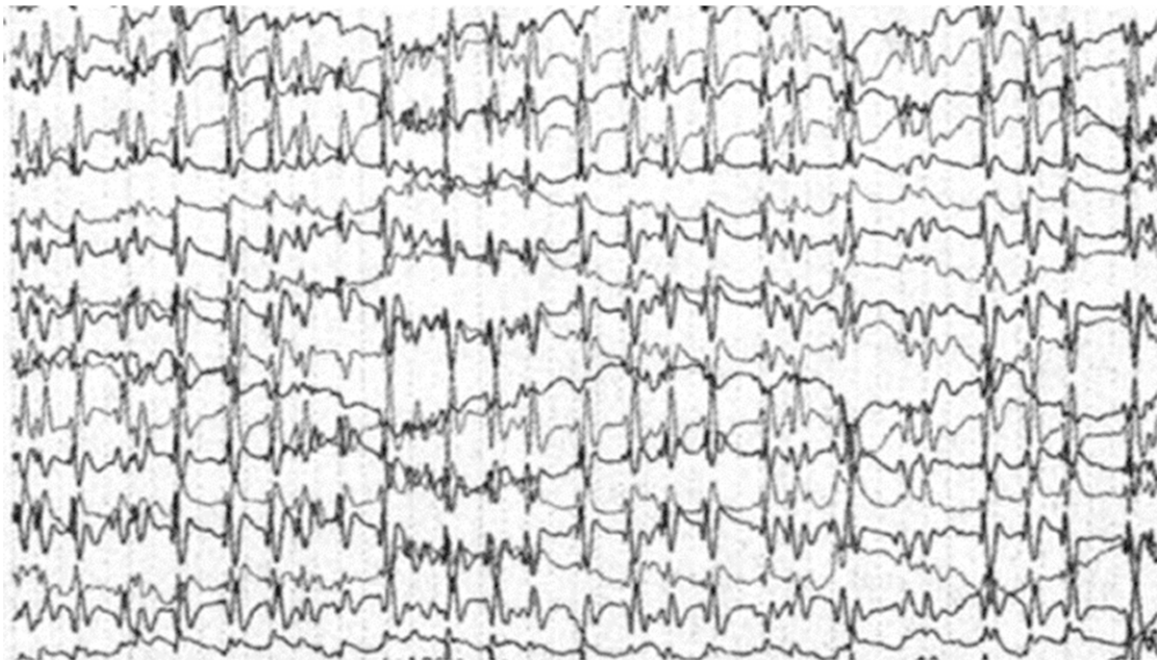

Figure 1. EEG performance at slow wave sleep stage in 1 case of CSWS patient. The electrical status epilepticus during sleep phenomenon appeared with the spike-wave index more than 85%.

sodes were 0~15 times, with different levels of intellectual and psychological abnormal behavior, language, motor and cognitive disorders. Of the 8 patients, 5 cases, among whom 3 had asphyxia, were with perinatal high-risk factors. Three cases were preterm infants associated with hypoxic-ischemic encephalopathy. Two cases had the history of febrile convulsion and 1 case had family history. Three cases had head CT scan and 5 cases received head MRI examination. Prior written informed consent was obtained from the guardian of the patients enrolled before undergoing the examination. The study protocol was approved by the ethical committee of Shanxi Province People's Hospital.

Diagnostic criteria

All patients met the diagnostic criteria of CSWS and the criteria were as follows: [1] childhood onset; [2] mainly the nocturnal paroxysmal epilepsy with various forms of epilepsy except the strong straight; [3] electroencephalogram (EEG) displays as wide range of spike and wave discharge with the discharge index ≥ 85%; [4] EEG shows focal or extensive spike slow wave while awake; [5] often have different degrees of cognitive, language and motor function damage; [6] the prognosis is good, and seizures and spike and wave discharges stop in adolescence (age above 20); [7] secondary obvious diffuse spike and slow wave complex is excluded .

Electroencephalography

The 8 cases of children admitted to hospital received video EEG ≥ 2 times, ≥ 2 h each time, or prolonged monitoring EEG longer than 22 h. The recording electrodes of EEG were placed in accordance with international standards of 10-20 system with 16 lead electrocardiogram and the bilateral ear electrodes was considered as reference electrode. Electroencephalography was performed while natural sleep or sleep induced with drugs (10 chloral hydrate 0.5 ml/Kg). Routine flash stimulation and hyperventilation induced test were conducted and the time including awake and at least 1 complete sleep cycle was recorded [3-5]. Follow-up of video EGG or dynamic EGG was carried every 3 months to 6 months.

Medication schedule

After admission, antiepileptic drugs were administrated [5-7]. Valproic acid combined with clonazepam was used in 4 cases. Lamotrigine in addition to valproic acid and clonazepam was used in the other 4 cases. The 8 patients

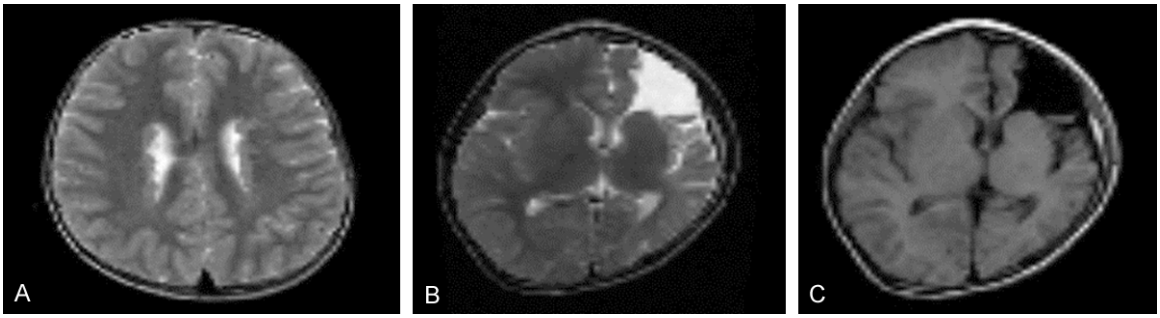

Figure 2. CT examination of 3 cases of CSWS patients. A. Global cerebral dysplasia with porencephaly. B. Cerebral dysplasia on the right brain. C. Brain atrophy on the right side.

all received hormone treatment and the therapeutic strategy was as follows. Three days of continuous pulse therapy of intravenous methylprednisolone (20 mg/(kg d)) was performed, followed by prednisone, orally taken, 1.5-2 mg/(kg d) for 1 moth and 1-1.5 mg/(kg d) for 1 month, respectively, and then the doses of hormone were gradually reduced. The treatment course lasted for 3-6 months. Antiepileptic drugs were taken continuously after discharge and 4 cases had taken oral prednisone for sequential treatment.

Results

EEG features

To determine the type of epilepsy and evaluate the effectiveness of the different drugs, EEG was carried out. Among the 8 patients (**Table 1**), 5 cases were with normal EEG background activity, 2 cases with occipital rhythm slow and 1 case with reduced amplitude of left brain electrical activity. By video EEG monitoring, frequent absence seizures with simultaneous EEG 1.5~3.5 Hz spike wave discharged was found in 1 case while awake and no seizure was monitored in the other 7 cases. Bipolar lead ESES was observed in slow wave sleep (non-rapid eye movement (NREM) stage) in all the 8 cases with the discharge index of more than 85% (**Figure 1**). And, the ESES was confined to the anterior head in 3 cases. However, no clinical seizures appeared in video surveillance. During rapid eye movement (REM), generalized spike wave disappeared, paroxysmal or focal slow wave occasionally occurred and sleep spindle activity all reduced. The EEG background rhythm when awake was normal. After awake, there was spike wave discharge or focal slow wave. These results indicated that the EEG background rhythm was basically normal in recovery period, and spike wave discharges or focal slow wave appeared while awake.

Clinical features

Each disease has unique clinical features of its own and these features are important resources for the study on development and treatment of the diseases [8]. Thus, clinical features was observed and recorded for further diagnosis and treatment. All the patients enrolled had epileptic seizures, as described by Qihua Zuo et al. [9-12]. The epileptic seizure types included generalized clonic seizures, tonic clonic seizures, myoclonic absence seizures, absence seizures and one side of limb clonus and orofacial seizures. However, no tonic seizures were detected. Various degrees of neuropsychiatric damage including speech disorder, temporal orientation decline, memory loss, learning disabilities, decreased concentration, hyperactivity, irritability, aggression and other behavioral disorders existed in all the patients and their intelligence quotient was below normal levels. These clinical features were important for diagnosis and treatment of epileptic seizure [13].

Neuroimaging features

To reveal whether there were lesions in the brain, CT and MRI scans were performed. Among them, 3 patients received head CT scan (**Figure 2**) and 5 patients received head MRI scan (**Figure 3**). Five cases had abnormal brain lesions while the other 3 had no obvious abnormal imaging. The lesions included diffuse or unilateral atelencephalia or brain atrophy, porencephaly and heterotopic gray matter. These results indicate that lesions often exist but not necessarily exist in CSWS patients.

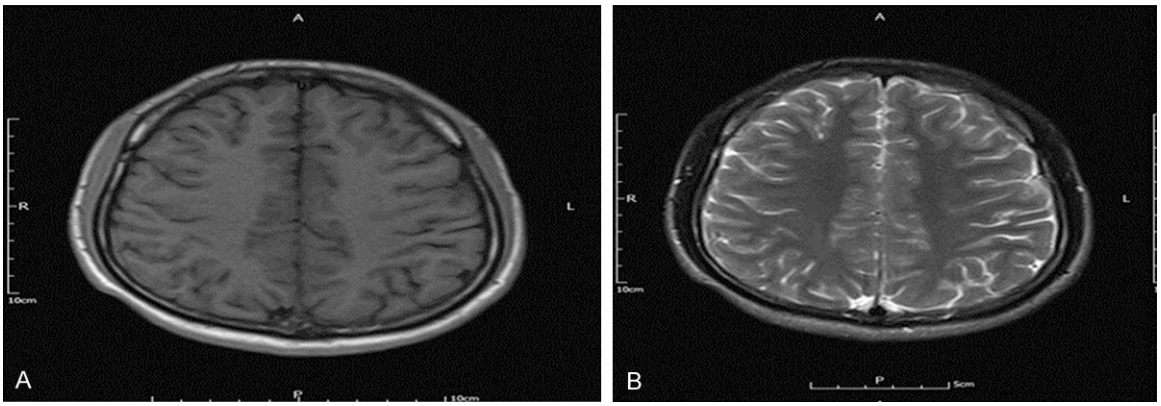

Figure 3. MRI examination pictures of 2 of the 5 cases of epilepsy patients with porencephaly. A. The MRI examination in epilepsy patients with heterotopic gray matter. B. The MRI examination in epilepsy patients with one side of cerebral dysgenesis.

The prognosis

To evaluate the effectiveness of the treatment and assess the prognosis, relevant follow-up studies were carried out. At the time of discharge, 2 cases were without clinical seizures. The seizures in the other 6 cases had reduced more than 75% with the seizure degree significantly reduced and the duration of seizure significantly shortened. Video EEG showed that all the 8 patients improved in varying degrees. The 2 cases of patients who only took anti epileptic drugs still had clinical seizures. However, the frequency of seizures was reduced and spine slow wave index (SWI) of NREM was about 70%. However, after 9 months, the frequency of seizures increased and the symptoms repeated. Thus, hormonal pulse therapy was performed. At the end of 1 year follow-up, seizures disappeared in 2 cases. No seizure appeared in the 4 cases who had taken hormonal therapy. The SWI of NREM was about 50% and epileptiform discharges disappeared after 1.5 years of therapy. EEG and cognitive ability had been obviously improved 3 months after treatment in these 4 cases. These results indicate that the prognosis of patients enrolled in this study is good.

Discussion

CSWS, a childhood special syndromes with the onset age ranged from 2 months to 12 years and the peak age ranged from 4 to 8 years, occurs mostly in boys. Before onset, the neurological and mental development is normal in majority of the patients. After onset, however, 33%-50% of the patients are found with abnormal nerve system or neural imaging and some are with cerebral palsy or other static encephalopathy [14]. Once the patients receive therapy, the clinical symptoms reduces, and, the psychological and learning function improves significantly. However, SWI of NREM in EEG is not significantly decreased, which, might be closely related to the abnormal brain structure. After onset of CSWS, comprehensive slowing, stagnation or retrogression of psychomotor development, and especially decrease in intelligence and spatial skills will appear. In clinic, CSWS is usually diagnosed as epileptic brain damage or other epilepsy syndrome [15]. In this study, 2 cases were diagnosed as symptomatic epilepsy. However, CSWS was ignored, which lead to clinical exacerbations. Typical epileptic seizure is considered as part of motor seizures or generalized seizures at night while seizure associated with fall is the feature of CSWS. Therefore, fall during seizures is an important characteristic that could be used for clinical diagnosis of CSWS.

The EEG features of CSWS are characterized by ESES phenomenon during slow wave sleep with decreased spindle waves especially in the fore head. This phenomenon is most obvious at the first stage of NREM during sleep and SWI is the highest. The index of SWI during the subsequent NREM fluctuates [16-20]. The 8 patients in this study were all with the characteristics of EEG changes of CSWS. They had only taken routine EEG examination, which, to some extent, resulted in delayed and improper diagnosis and treatment. So, it is recommended

that EEG monitoring of complete sleep cycle should be performed in patients with multiple forms of epilepsy and stagnation or retrogression in intelligent and physical development [21].

Mental and behavioral disorders of CSWS patients still exist after the disappearance of ESES. And, the severity and the duration are associated with those of ESES. Thus, early effective treatment to improve ESES is necessary for neuropsychiatric symptoms improvement [8]. At present, for the treatment of CSWS, in addition to anti epileptic drugs, immunoglobulin, ketosis diet and surgical operation treatment are still under study. Hormone can reduce seizures and SWI of EEG, thus further improving the patients' cognitive ability. Although the mechanism, the specific course of action and the amount are still under investigation, the effect has been more and more affirmed. It is reported that the clinical symptoms of CSWS significantly improves after 3 months of hormone treatment and the recurrent patients are commonly those without hormone treatment or irregular users. In this study, methylprednisolone pulse and prednisone sequential treatment was performed and the clinical symptoms of all the 8 patients were improved in short term. Confirmed improvement of cognitive function and EEG was observed after 3 months in 4 cases. Two patients (case #?) relapsed 9 months after the first use of methylprednisolone and satisfactory effects was obtained with the maintaining of the original antiepileptic drugs treatment and reapplication of hormone therapy. After 8 months, the epileptiform discharge disappeared and this further confirmed that hormone was one of the important means that could effectively treating CSWS [22]. With the combined application of valproic acid, clonazepam, lamotrigine and hormone, seizures of the children significantly reduced and EEG significantly improved. This might be because that hormone could prolong the half life of drugs, improve the blood drug concentration, enhance postsynaptic action, inhibit the release of excitatory amino acids and maintain the stable membrane potential, thus controlling seizures and suppressing epileptic electrical activity.

In conclusion, in this study, by retrospective analysis, we confirmed that fall during seizures is an important characteristic that could be used for early clinical diagnosis of CSWS. For the patients those with multiple forms of epilepsy and stagnation or retrogression in intelligent and physical development, not only EEG but monitoring EEG should be performed in order to avoid misdiagnosis. Hormone, combined with antiepileptic drugs had good effect on the treatment and the prognosis of CSWS.

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Disclosure of conflict of interest

None.

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