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Different Outcome with Different Aetiologies: The Prognosis Follow-up in 13 Infants with Burst-suppression Pattern

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Abstract ***Purpose:*** Burst-suppression is an electroencephalogram (EEG) pattern which can be caused by various aetiologies and with poor outcome. The aim of our study was to investigate the outcome of children with burst-suppression pattern on EEG accompanied with different aetiologies. ***Methods:*** There were 13 infants with burst-suppression pattern on EEG included in our study, eight cases were diagnosed as Ohtahara syndrome (OS), while other four cases were diagnosed as early myoclonic encephalopathy (EME) and one case was diagnosed as hypoxic-ischaemic encephalopathy (HIE). All patients were followed up for eight months to two years, including the clinical evaluation and the EEG registration every three months. ***Findings*:** OS and EME were two common diseases associated with burst-suppression pattern. Partial seizure was the most common seizure type in all burst-suppression pattern patients. And spasm was more often in OS patients while myoclonia was common in EME patients. The period of burst-suppression pattern on EEG was several months in all OS and EME patients, while which was less than two weeks in one HIE patient. The HIE patient had the best outcome while the EME patients had the worst outcome in these patients. The prognosis in OS patients is in between the HIE patient and EME patients. ***Conclusions:*** The outcome of development and cognition were poor in most of burst-suppression patients. The prognosis was different with different aetiologies. The aetiology and the rapidity of EEG improvement affected the outcome.

Key words Burst-suppression; Early myoclonic encephalopathy; Neurologic outcome; Ohtahara syndrome

Introduction

Burst-suppression is a special electroencephalogram (EEG) pattern in which high voltage activity (burst) and flat (suppression) periods alternate systematically,[1] which can be caused by various aetiologies. Burst-suppression was first found in the states of deep anesthesia and sedative, and later was observed in childhood epilepsy encephalopathy, cerebral anoxia, and other causes (drug-related intoxication, hypothermia, and so on).[1,2] No matter what aetiology, burst-suppression pattern was considered as the manifestation of severe brain damage and had poor prognosis.[3] Most of studies had showed that patients with a burst-suppression EEG pattern had a high mortality and morbidity.[4,5] But some other studies had demonstrated that the burst-suppression pattern was reversible in some situations and the prognosis of these patients was not so poor as we considered before. Such as in the study by Douglass et al,[6] they found that the prognosis was not so poor in patients who had a reversible burst-suppression pattern.

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From the previous studies we can concluded that the longer inter-burst intervals in an EEG recording (longer than 30s),[7] consistent background EEG abnormalities and the amplitude of the electrical activity between the bursts[8,9] were usually associated with unfavourable outcome. On the other hand, the reactive burst-suppression pattern[6] and reversible burst-suppression pattern[6] were associated with better outcome. But the data was rare and the conclusion was controversial.[10]

So in our study, we evaluate the clinical and EEG characteristics of patients with burst-suppression pattern on EEG registration and followed-up the prognosis of these patients with different aetiologies, try to investigate the prognosis of different aetiologies with burst-suppression pattern and find some clues to predict the prognosis.

Materials and Methods

There were 13 patients with burst-suppression pattern on EEG registration included in our study and were followed-up at the Department of Pediatric Neurology, Children's Hospital of Zhejiang University in China from March 2009 to March 2013. All patients were coincided with these criteria: (1) All patients underwent a VEEG registration (the sleep EEG with the video registration for two-hour duration) and were carried out repeatedly in 24 hours later, both VEEG monitoring showed burst-suppression pattern. (2) Besides the EEG analysis, all patients received clinical evaluation including history, physical and neurological examinations, brain magnetic resonance imaging (MRI). (3) All patients were followed-up for eight months to two years, including the clinical evaluation, neuropsychological evaluation and the EEG registration every three months. (4) The definition of burst -suppression pattern was: the periods of flat background that may last from 2-10 seconds, interrupted by high voltage bursts (consisting of variable amounts of spikes and sharps waves with irregular delta and theta waves) lasting 1-10 seconds.[9] (5) The other reasons for burst-suppression pattern, such as drug-related intoxication (for example, high dose phenobarbital), hypothermia and deep general anesthesia were excluded in all patients.

We used sixteen channels in EEG registration according to the international 10-20 system. The research was approved by a human experimentation ethics committee. All patients provided informed consent for using their information in our study.

Results

1. Gender and the Onset Age

In our study, 13 infants were included, seven male patients and six female patients, no sex differences. All patients presented the manifestation in little baby younger than two months old, 10 of them were newborn babies and the youngest baby was on the first day of life. The onset age was range from one day to two months, and the average age was 18.2 days (Table 1). Two patients had family history of epilepsy and other two cases had asphyxia history when on delivery.

2. Diagnosis and Antiepileptic Drugs

There were eight cases diagnosed as Early-infantile epileptic encephalopathy with burst-suppression which was also named as Ohtahara syndrome (OS), while other four cases were diagnosed as early myoclonic encephalopathy (EME) and one case was diagnosed as hypoxic-ischaemic encephalopathy (HIE)(Table 1). The name and the dosage of antiepileptic drugs used in each patient were listed in Table 1. Phenobarbital was used in small dosage (5 mg/kg/d, three days) only in patient 13. All VEEG registrations were carried out before the patients accepted the antiepileptic drugs. So we excluded the drug effect on the EEG manifestation.

3. Neuroimaging and Laboratory Findings

All patients underwent head MRI examinations and metabolic check. MRI scans showed structural abnormalities in three cases, one hemimegalencephaly (case 2) and one white matter abnormal signal (case 4) in OS patients, one diffuse hypoxic-ischaemic change in HIE patient (case 13). Other two cases showed inborn metabolic diseases, both of whom happened in EME patients.

4. The Onset Seizure Types

The patients had different attack forms, there were only one attack at the onset of symptoms in seven patients while the other six patients had two types of seizures. The most prevalent type of seizures was partial seizures, which was seen in 11 patients. Partial seizures and myoclonias were two common seizure types in four EME patients while partial seizures, focal tonic and tonic spasms were the most common seizure types in eight OS patients. The duration of the attacks lasted from several seconds to two minutes and the daily seizure frequency was ranging from five to

300, the myoclonias and the spasms often occurred in clusters.

5. Initial EEG Check

All children carried out VEEG monitoring twice and both showed burst-suppression pattern on EEG. The burst-suppression pattern presented in both awake and sleepy in nine patients while only happened in sleepy stage in other four children.

6. Prognosis and EEG Follow-up

There were 12 cases suffered refractory seizures besides one HIE patient (case 13) whose seizure was controlled easily. The seizure types had changed in eight patients. All happened between two months to six months. All three tonic seizures disappeared in three to six months after seizure onset. The spasm was the most common second type of seizures and happened in four cases. Fragmentary myoclonia was seen in one patient in about 10 days after

Table 1 Clinical characteristics of all suppression-burst patients

Case	Onset age (day)	Gender	Diagnosis	Family history	Head MRI	Metabolism check	AEDs
1	1	Male	OS	Negative	Normal	Normal	TPM (3 mg/kg/d) VPA (36 mg/ke/d)
2	9	Male	OS	Positive	Hemimegalencephaly	Normal	TPM (4.5 mg/kg/d) VPA (25 mg/kg/d) LEV (30 mg/kg/d)
3	15	Male	EME	Negative	Normal	Abnormal	ACTH TPM (5 mg/kg/d) LEV (45 mg/kg/d)
4	20	Female	OS	Negative	White-matter abnormal signal	Normal	ACTH TPM (3.6 mg/kg/d) VPA (40 mg/kg/d)
5	1	Female	EME	Negative	Normal	abnormal	TPM (6 mg/kg/d) LEV (35 mg/kg/d)
6	11	Female	EME	Negative	Normal	Normal	TPM (3 mg/kg/d) CZP
7	1	Male	EME	Negative	Normal	Normal	Steroids TPM (4.2 mg/kg/d) LEV (45 mg/kg/d)
8	15	Female	OS	Negative	Normal	Normal	Steroids VPA (32 mg/kg/d) CZP
9	55	Male	OS	Negative	Normal	Normal	VPA (48 mg/kg/d) CZP ACTH
10	1	Female	OS	Positive	Normal	Normal	VPA (30 mg/kg/d) TPM (2.5 mg/kg/d)
11	46	Male	OS	Negative	Normal	Normal	TPM (3.8 mg/kg/d) Steroids
12	60	Female	OS	Negative	Normal	Normal	TPM (3 mg/kg/d) LEV (40 mg/kg/d)
13	2	Male	HIE	Negative	Normal	Normal	PB (5 mg/kg/d bid x 3 days)

MRI, magnetic resonance imaging; AEDs, antiepiletic drugs; OS, Ohtahara syndrome; EME, early myoclonic encephalopathy; HIE, hypoxic-ischaemic encephalopathy; PB, phenobarbital; VPA, valproate; CZP, clonazepam; TPM, topiramate; LEV, levetiracetam; ACTH, adrenocorticotrophic hormone

the onset of partial seizure. One generalised tonic-clonic seizure and one partial seizure as the second seizure type were observed in patients when followed-up for about six months.

The outcome of development was poor in most of these patients. The HIE patient had only mild impair of language in two years old and the motor development was normal. The other 12 patients with epileptic encephalopathies all had moderate to severe neuropsychological deficits and motor delay. The EME patients had the worst outcome because all four EME patients had severe nervous system sequelae and all died before one year old. In eight OS patients, every child had moderate to severe neuropsychological impairs. There were five patients couldn't walk and seven patients had language delayed. Four of these eight OS patients developed to West syndrome in less than six months old and one transferred to Lennox-Gastaut syndrome while in two years old.

When VEEG scan were carried out two weeks after inclusion, the EEG had become normal in HIE patient (case 13) while the other 12 patients still showed burst-suppression pattern. The VEEG monitoring of case 13 always showed normal during the entire follow-up period. There were four cases stilled showed burst-suppression pattern on EEG when followed-up for three months. Burst-suppression pattern on EEG were all disappeared in less than six months in all 12 patients. Four in other twelve patients were developed hypsarrhythmia during three to six months when followed-up. All other 12 patients showed multi-foci epileptic discharges on VEEG after one year followed-up.

Discussion

In this paper we have reviewed clinical and EEG characteristics and followed-up the prognosis of patients with burst-suppression pattern on EEG registration caused by different aetiologies. As expected we have found that most of these patients had unfavourable outcome.

Table 2 Seizure types of all suppression-burst patients

Case	Seizure types (onset)	Seizure types (change)	Frequency	Last time of seizure (second)
1	Tonic Partial seizure	Partial seizure (4 months)	10	10-20
2	Tonic	Spasm (3 months)	10-20	2-3
3	Partial seizure	Partial seizure Myoclonias (10 days)	50-100	7-8
4	Partial seizure Spasm	No change	4-5	10-15
5	Partial seizure	Generalizedtonic-clonic seizure (6 months)	3-4	5-6
6	Partial seizure Myoclonias	No change	40-50	10-60
7	Partial seizure Myoclonias	No change	30-50	10-40
8	Tonic Spasm	Partial seizure (6 months) Spasm	15-20	5-10
9	Partial seizure	Spasm (4 months)	50-100	10-120
10	Partial seizure	Partial seizure Spasm (5 months)	7-8	10-20
11	Partial seizure Spasm	No change	100-300	2-5
12	Partial seizure	Partial seizure Spasm (4 months)	2-3	10-20
13	Partial seizure	Seizure free	4-5	5-10

There were three diseases referred to burst-suppression pattern in our study. OS and EME were the most two common epileptic encephalopathies associated with burst-suppression pattern. The burst-suppression pattern on EEG must persist for more than two weeks in epileptic encephalopathy while which persists for less than two weeks in other transient conditions.[11] In our study, the period of burst-suppression pattern on EEG was more than two weeks (less than six months) in all OS and EME patients, while which was less than two weeks in one HIE patient.

OS is characterised by epileptic spasms in clusters and burst-suppression pattern on EEG both during wakefulness and sleep. In some cases it proceeds from OS to West syndrome in middle infancy and from West syndrome to Lennox-Gastaut syndrome later. Meanwhile, the characteristics features of EME are myoclonias, partial seizures and burst-suppression pattern which becomes apparent in sleepy.[12] But sometimes it is difficult to make diagnosis because lack of the typical clinic features.[13] In our study, partial seizure was the most common seizure type in all burst-suppression pattern patients. Besides that, spasm was more often in OS patients while myoclonias was common in EME patients. Half of eight OS patients developed to West syndrome and one in them transferred to Lennox-Gastaut syndrome later. That was coincident with previous data.

In general, EEG burst-suppression is often associated with

Table 3 Follow-up data of all suppression-burst patients

Case	Electroencephalogram follow-up			Seizure and prognosis follow-up		
	Three months	Six months	One year	Six months	One year	Two years
1	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Seizure	Seizure	Seizure
2	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Seizure	Seizure	Seizure free
3	Burst-suppression	Multi-foci epileptic discharges	–	Seizure	Die (10-month old)	–
4	Hypsarrhythmia	Hypsarrhythmia	Multi-foci epileptic discharges	Seizure and West syndrome	Seizure free	Seizure free
5	Multi-foci epileptic discharges	Multi-foci epileptic discharges	–	Seizure	Die (1-year old)	–
6	Multi-foci epileptic discharges	Multi-foci epileptic discharges	–	Seizure	Die (8-month old)	–
7	Burst-suppression	Multi-foci epileptic discharges	–	Seizure	Die (1-year old)	–
8	Burst-suppression	Hypsarrhythmia	Multi-foci epileptic discharges	Seizure and West syndrome	Seizure	Seizure free
9	Burst-suppression	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Seizure	Seizure	Seizure free
10	Multi-foci epileptic discharges	Hypsarrhythmia	Multi-foci epileptic discharges	Seizure and West syndrome	Seizure	Seizure
11	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Seizure	Seizure	Seizure free
12	Hypsarrhythmia	Multi-foci epileptic discharges	Multi-foci epileptic discharges	Seizure and West syndrome	Seizure	Seizure and Lennox-Gastaut syndrome
13	Normal	Normal	Normal	Seizure free	Seizure free	Seizure free

"–" means drop out when followed-up.

severe cerebral damage that can be observed in different aetiologies and it usually indicates a poor prognosis. The mechanism of burst suppression is not clear. Though burst-suppression EEG pattern was considered as risk factors of bad outcome many times, in some cases this EEG pattern was reversible and the prognosis was not so poor.[3]

There were three aetiologies referred to in our study, and the prognosis was different with different aetiologies respectively. The other aetiologies (such as the use of high dose phenobarbital, hypothermia and so on) which will cause the burst-suppression EEG pattern were excluded. The HIE patient had the best outcome while the EME patients had the worst outcome in these patients. Besides the mild speech deficit, the motor development was normal and the seizures were easily controlled in one HIE patient. All four EME patients died in less than one year old age. The prognosis in OS patients is in between the HIE patient and EME patients. The OS patients had refractory seizures and moderate to severe cognition impairment and/or motor development delay. We also found that the burst suppression pattern in HIE patient improved in two weeks while the burst suppression pattern all lasted long time in other OS and EME patients. It indicated that the HIE patient had the best outcome and best recovery of EEG manifestation. The OS and EME patients had poor outcome and poor reversible of EEG manifestations. We concluded that the prognosis of burst-suppression pattern was referred to aetiology and the rapidity of EEG improvement. This conclusion was coincident with previous research.

So it is not always accuracy that burst-suppression pattern in EEG monitoring indicate the poor prognosis. The prognosis is not only with the aetiology but also with the duration of burst-suppression pattern. Graziani et al found that a single EEG monitoring with burst-suppression pattern in near term infants often led to erroneous value of predict the outcome.[14] So a serial EEG follow-up was more valuable than only single monitoring in predict the outcome. Douglass et al concluded that the reactive burst-suppression pattern was referred to a better outcome.[6] Takeuchi and Watanabe found that the rapidity of EEG improvement helped to predict outcome and the prognosis was better if the EEG improved in 3 weeks.[15] So according to our study and previous data, it is concluded that if EEG burst-suppression pattern improved in two to three weeks, the prognosis is better. And if EEG burst suppression pattern persist, it may indicate poor outcome.

Besides that, there are some other factors affect the outcome of patients with burst-suppression pattern. Some researchers found the duration of the inter burst interval[16] whereas others concluded the amplitude of the electrical activity between the bursts[8,9] affect the prognosis. One limitation in our study is that we didn't investigate the other predict factors. The other limitation of our study is the serial number was small. So it need more largely and insight study in the future.

This study brings the investigation of the EEG and clinical features of patients with burst-suppression pattern and study the prognosis of these patients. In our study, OS and EME were the most common diseases of burst-suppression pattern. It can also seen in severe HIE patients. Although most of infants with burst-suppression pattern had poor neurologic outcome, the prognosis was different with different aetiologies. The aetiology and the rapidity of EEG improvement affected the outcome. Furthermore, the more detailed EEG analysis and the large research are needed.

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Declaration of Interest

We declare that we have no conflict of interests.

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