Original Research Article

Differential diagnosis of nonepileptic twilight state with convulsive manifestations after febrile seizures

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Potential Conflict of Interest Report

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Abstract

Background: Nonepileptic twilight state with convulsive manifestations (NETC) is a nonepileptic state following a febrile seizure (FS), which may be misdiagnosed as a prolonged seizure and result in overtreatment. We aimed to describe clinical manifestations of NETC and to determine characteristics that are helpful to distinguish NETC from other pathological conditions.

Methods: We conducted a retrospective chart review from January 2010 to December 2016 and selected the patients who presented with symptoms resembling status epilepticus with fever and a confirmed diagnosis using an electroencephalogram (EEG). We compared the NETC clinical features and venous blood gas analysis results with those of other conditions that mimic NETC. We also compared the characteristics of NETC with past reports.

Results: Our NETC patients presented with short durations of the preceding generalized convulsions followed by tonic posturing, closed eyes, no cyanosis, responsiveness to painful stimulation, and no accumulation of CO_2 in the venous blood gas. Most of these characteristics were consistent with past reports. Prolonged FS or acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) showed several of these features, but all the characteristics were not consistent with our study.

Conclusions: Prolonged FS and AESD need to be differentiated from NETC, and close clinical observation makes it possible to partially distinguish NETC from the other conditions. EEG is recommended for patients with symptoms that are inconsistent with these features.

Key Words

prolonged febrile seizure; acute encephalopathy with biphasic seizures and late reduced diffusion; venous blood gas analysis; electroencephalogram; clinical characteristics; venous blood gas

1. Introduction

Nonepileptic twilight state with convulsive manifestations (NETC) is reported for postictal status with symptoms that resemble prolonged febrile seizures (FSs), such as tonic posturing and eye deviation following a FS [1, 2]. Although NETC is reported to be a nonepileptic state that often continues for more than 30 minutes, but which requires no treatment [2], it is estimated that NETC is frequently misdiagnosed as prolonged FS and is thus treated with intravenous antiepileptic drugs, leading to overtreatment. Even though several clinical features of NETC such as tonic posturing or lack of cyanosis were elucidated [1, 2], there are still few reports about NETC, and distinguishing NETCs from prolonged seizures or other pathological conditions remains difficult. There is a need to at least partially differentiate NETC from other conditions without using an electroencephalogram (EEG) in emergency rooms.

We report differences between clinical manifestations and EEG findings in NETC after FS and in other conditions with clinically similar presentations. We also compare our patients' NETC symptoms with those of past reports.

2. Methods

We retrospectively reviewed clinical records of patients transferred to Kurashiki Central Hospital from January 2010 to December 2016. We examined the patients presenting with symptoms resembling status epilepticus with fever, in whom an EEG was performed to confirm a diagnosis. We

excluded patients with known epilepsy and central nervous system infections. In addition to whether patients showed closed eyes, tonic posturing, and cyanosis, we assessed reaction to painful stimuli, duration of the preceding generalized convulsions, the time required for spontaneous eye opening, and findings of venous blood gas analysis. We made a diagnosis of NETC when no ictal patterns were found in EEG, as previously defined by Yamamoto [2], and consciousness was completely recovered without sequelae. This study was approved by the Kurashiki Central Hospital Ethics Committee.

3. Results

3-1. Clinical observations

During the observation period, 30 patients were clinically suspected as having status epilepticus with fever, and EEG was recorded to confirm diagnosis in six patients. Because no patients fulfilled the exclusion criteria, we analyzed the data from all six patients.

Diagnosis of the six patients was as follows: patients 1 to 3 had NETC, patients 4 and 5 had a prolonged FS, and patient 6 had acute encephalopathy with biphasic seizures and late reduced diffusion (AESD).

In patients with NETC, the preceding generalized seizure continued for no more than 5 minutes and tonic posturing followed for over 30 minutes. During NETC, eyes were closed and no cyanosis was found, as reported previously [1, 2] (Table 1). Tonic posturing became gradually intermittent and vanished. Additionally, all patients responded to painful stimuli, including crying,

and venous blood gas analysis showed normal pH and pCO_2 levels. Two of the three patients with NETC regained consciousness within 12 hours and became alert thereafter (Table 1). The remaining patient was initially misdiagnosed as having a prolonged FS and was treated with antiepileptic drugs that were ineffective.

For patients 4 and 5 with a prolonged FS, seizures were accompanied by cyanosis and CO_2 accumulation in venous blood gas. In patient 4, the seizure began with a generalized convulsion lasting for approximately 5 minutes followed by impaired consciousness. The second generalized seizure occurred 50 minutes after the first seizure and it lasted for a few minutes. When the patient was transferred to our hospital, his eyes were closed, there was generalized loss of muscle tone and no response to painful stimulation, and respiratory acidosis was indicated in the venous blood gas analysis results (Table 1). Tachycardia continued despite intravenous fluid infusion and loss of consciousness and hypoventilation also persisted. Prolonged FS was suspected and diagnosed using an EEG. These symptoms improved after antiepileptic drugs were administered intravenously. For patient 5, a FS started with a convulsion involving the right upper limb, and when he was transferred to our hospital, twitching of bilateral eyelids was also found. Convulsions of the right upper limb lasted for 4 hours before it was controlled by intravenous antiepileptic drugs (Table 1).

Patient 6 was diagnosed with AESD. The preceding generalized convulsion lasted for more than 30 minutes with cyanosis. After the generalized convulsion was suppressed by intravenous antiepileptic drugs, tonic posturing continued intermittently while the eyes were closed and cyanosis

gradually improved (Table 1). This patient showed a reaction to painful stimulation by moving all limbs, but there was no crying. Severe acidosis and CO_2 accumulation were detected by venous blood gas analysis performed immediately after the generalized convulsion (Table 1). Although the patient became partially responsive 5 hours after admission, impaired consciousness continued and oral dyskinesia and perseveration were found 12 hours after admission. His consciousness did not improve significantly, and the second seizure occurred on the fifth day after admission. A brain MRI showed a bright tree appearance, which means restricted diffusion involving subcortical white matter [3], leading to a diagnosis of AESD. This patient subsequently developed refractory epilepsy.

3.2. EEG findings

In patients with NETC, EEG showed posterior head area dominant high-voltage delta and theta waves (Fig. 1A). A mixture of lower-amplitude theta and alpha waves were seen intermittently. In patient 1, this lower-amplitude pattern (Fig. 1B) gradually increased before he woke up. The EEG showed no change that was consistent with tonic posturing.

Two patients were diagnosed with prolonged FS via EEG findings. The EEG of patient 4 exhibited diffuse, continuous spike-and-wave discharges representing a continuing seizure (Fig. 1C). These discharges were suppressed by intravenous antiepileptic drugs, followed by high-amplitude, diffuse delta waves (Fig. 1D). These slow waves gradually diminished in accordance with consciousness improvement. Patient 5 was diagnosed with focal status epilepticus because the EEG

showed continuous spike-and-wave discharges mainly over the left hemisphere, which was controlled by intravenous antiepileptic drugs; however, further information was unavailable because no subsequent EEG recording was conducted.

The EEG findings in the patient with AESD showed high-amplitude and diffuse slow wave activities immediately after the generalized convulsion was terminated (Fig. 1E). EEG did not change in accordance with intermittent tonic posturing as mentioned above. At 5 hours after admission, although the amount of faster and lower-voltage waves increased compared with the EEG immediately after the generalized convulsion, alpha activity was rarely found (Fig. 1F). Subsequently, EEG findings did not improve significantly and the second seizure eventually occurred.

4. Discussion

In our study, clinical presentation of the patients with prolonged FS and AESD were similar to that of patients with NETC, but careful observation distinguished between them to some extent.

The clinical features of patients with NETC in our study were tonic posturing and lack of cyanosis, as reported previously [1, 2]. Additionally, all patients had closed eyes and cried upon painful stimulation, as described by Specchio et al. [1]. Including our two patients, most of the reported patients presented with generalized motor seizures lasting to within a few minutes before NETC. Although a patient with generalized loss of muscle tone preceding NETC and two patients with focal clonic movements during NETC were reported by Yamamoto [2], these symptoms were not found in

our patients or in the patient cases reported by Specchio et al. [1]. No studies have discussed venous blood gas analysis, and we found no abnormality in pH or CO_2 accumulation in a venous blood gas analysis. In our study, the EEG demonstrated a mixture of diffuse delta or theta waves with posterior dominancy, as described by Specchio et al. [1]. No obvious EEG changes were found in accordance with tonic posturing in our report, even though Yamamoto reported a diffuse rhythmic theta pattern that tended to increase as the clinical manifestations became more intense. We did not use antiepileptic drugs for the two patients who were diagnosed initially with NETC, leading to a full recovery within 12 hours. However, the other patient was misdiagnosed with prolonged FS and initially and treated with antiepileptic drugs, which had no effect; this is in agreement with past reports [1, 2], indicating the importance of an accurate NETC diagnosis.

Two of our patients had prolonged FS with no prolonged generalized convulsion. For patient 4, the seizure started with a generalized convulsion that lasted about 5 minutes and his eyes were closed when he was transferred to our hospital, which suggested NETC as a differential diagnosis. However, cyanosis and CO_2 accumulation in venous blood in addition to no reaction to painful stimulation were atypical for NETC. In patient 5, the seizure started with a convulsion in the right upper limb with cyanosis, and the convulsion remained focal during the seizure. CO_2 accumulation was found in both patients in venous blood gas analysis. Persistent cyanosis and CO_2 accumulation were helpful to distinguish between prolonged FS and NETC.

Although the patient with AESD showed similar characteristics as patients with NETC after

a generalized convulsion in our study, the duration of the generalized convulsion was significantly longer than those preceding NETC. Severe acidosis and CO_2 accumulation found in venous blood also reflected a prolonged generalized seizure. These findings were useful but the two conditions cannot be always distinguished by the duration of the preceding generalized convulsion, because some patients with AESD who present with generalized convulsions for a few minutes have been reported [4]. Currently, we cannot determine how useful the duration of generalized convulsion is in distinguishing AESD from NETC. In our patient, oral dyskinesia and perseveration were also found before the second convulsion, which suggests AESD [5]. However, in this patient, the time until spontaneous eye-opening was short compared with those with NETC, and consciousness impairment persisted thereafter. Prolonged disturbed consciousness was one of the features of AESD [6] and evaluating consciousness is also important to distinguish NETC from AESD. This point also highlights the importance of reducing unnecessary use of antiepileptic drugs. In EEG analysis, high-amplitude, diffuse slow wave activities were found immediately after the generalized convulsion, and although the amplitude decreased and the frequency of waves gradually increased, alpha activities were rarely seen, indicating AESD rather than NETC [7]. Although these findings were useful in distinguishing between AESD and NETC in our patients, patient 6 had severe AESD and the differences mentioned above might not always apply for patients with milder AESD.

There are limitations to this study. Because of the retrospective nature of this study, we found only six patients who fulfilled the inclusion criteria. A prospective study is required that enrolls a

larger number of patients. In our study, we focused on patients who presented with symptoms resembling status epilepticus, because we hoped to find a method to distinguish NETC from prolonged FS without using EEG and to reduce unnecessary use of antiepileptic drugs. Therefore, we did not include patients with prolonged impaired consciousness without other suspicious symptoms of status epilepticus after a FS as a differential diagnosis. Additionally, the EEG was performed in the emergency room, and we could not sufficiently evaluate this data; the number of EEG electrodes used was fewer than that for a regular EEG and we did not evaluate EEG changes associated with painful stimulation.

In conclusion, accurate diagnosis of NETC is needed because patients with NETC can be misdiagnosed as having prolonged FS and they are treated with unnecessary antiepileptic drugs, or AESD may be misdiagnosed as NETC. NETC patient cases were compared with prolonged FS and AESD patient cases in our study, and NETC typical symptoms were shown to shorten the duration of the generalized convulsion during fever followed by tonic posturing and responsiveness to painful stimulation and closed eyes and lack of cyanosis. Venous blood gas analysis is also useful for diagnosing NETC. Patients' symptoms that were not consistent with all the symptoms above may not have NETC, and EEG is recommended for accurate diagnosis and treatment.

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Figure legends

Figure 1. Electroencephalograms from a patient with nonepileptic twilight state with convulsive manifestations.

A) There is a mixture of posterior dominant high voltage delta and theta waves. B) Lower-amplitude epochs consisting of theta and alpha waves were seen intermittently and they became more abundant over time before the patient regained consciousness.

C), D) Electroencephalograms from a patient with a prolonged febrile seizure. C) There are diffuse, continuous spike-and-wave discharges indicating an ongoing seizure. D) There are diffuse high-amplitude delta waves after the seizure was terminated by the intravenous administration of antiepileptic drugs.

E), F) Electroencephalograms from a patient with acute encephalopathy with biphasic seizures and late reduced diffusion. E) There is high-voltage, diffuse delta activity immediately after the generalized convulsion was suppressed by intravenous antiepileptic drugs. F) The recording at 5 hours after admission showed a slight increase in faster and lower-voltage waves but alpha activity was rarely found.

Tables

Table 1. Clinical characteristics of the patients

Case	Age	Sex	Diagnosis	BT (°C)	Eyes	Eye deviation	Tonic posturing	Cyanosis	Time for opening eyes (h)	Duration of generalized convulsion (min)	EEG findings	pH	pCO2 (mmHg)	BE (mEq/L)	Number of intravenous AEDs
1	1	M	NETC	39.9	closed	-	+	-	4	< 5	Diffuse δ-θ	7.39	35	−3.3	0
2	1	M	NETC	39.9	closed	-	+	-	15	< 5	Diffuse δ-θ	7.37	38	−2.5	4
3	2	M	NETC	40.8	closed	-	+	-	9	< 5	Diffuse δ-θ	ND	ND	ND	0
4	1	M	Prolonged FS	38.3	closed	-	-	+	9	5	Diffuse sp-w	7.13	71	−7.3	2
5	3	M	Prolonged FS	38.0	open	+	+	+	11	0	Left-side dominant diffuse sp-w	ND	55	ND	2
6	2	M	AESD	39.0	closed	-	+	+	5	55	Diffuse δ	7.10	69	−10.9	2

M, male; F, female; BT, body temperature; NETC, nonepileptic twilight state with convulsive manifestations; FS, febrile seizure; AESD, acute encephalopathy with biphasic seizures with late restricted diffusion; BE, base excess; AEDs, antiepileptic drugs; sp-w, spike and waves; ND, no data