Original article

Epileptic Disord 2016; 18 (4): 399-407

Varied responses to benzodiazepine treatment in cephalosporin-related generalized periodic discharges

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Received July 24, 2015; Accepted July 16, 2016

ABSTRACT – Although benzodiazepines (BZDs) are used as the first-line treatment for status epilepticus, previous studies have shown inconsistent responses to BZDs in patients with cephalosporin-related non-convulsive status epilepticus. In this study, we investigated nine patients with cephalosporin-related impaired consciousness and their EEGs all showed generalized periodic discharges (GPDs). One of the patients received repetitive BZD injections without discontinuing cephalosporins, and neither his clinical symptoms nor GPDs on EEG responded to BZDs. Seven of the patients received BZDs after discontinuation of cephalosporins, but only two of them responded immediately to BZD administration. One of the patients did not receive BZDs or antiepileptic drugs, and this patient spontaneously recovered consciousness in one day after cephalosporins were discontinued. The changes in consciousness were reversible in all of the nine patients after cephalosporins were withdrawn. The administration of intravenous BZDs in cases with impairment of consciousness and GPDs secondary to cephalosporins may help in only a small number of patients. Cephalosporin withdrawal is ultimately mandatory in these patients.

Key words: generalized periodic discharge, cephalosporin, benzodiazepine, non-convulsive status epilepticus, encephalopathy

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doi:10.1684/epd.2016.0867

The cephalosporins are a class of beta-lactam antibiotics that are widely used and primarily eliminated by renal excretion. Cephalosporin-related encephalopathy (Jallon *et al.*, 2000; Garces *et al.*, 2008) and non-convulsive status epilepticus (NCSE; Martínez-Rodríguez *et al.*, 2001; Fernández-Torre *et al.*, 2005; Maganti *et al.*, 2006; Thabet *et al.*, 2009) have been reported in recent years,

especially in patients with impaired renal function (Martínez-Rodríguez *et al.*, 2001; Garces *et al.*, 2008). The EEG presentations of these patients can vary from diffuse slow waves, triphasic waves, to generalized or multifocal high-voltage sharp activities or sharp and slow waves presenting with periodic or semi-periodic patterns. The generalized sharp activities have been viewed as an epileptic discharge, characteristic of NCSE by many previous reports, and patients displaying this pattern are commonly treated with benzodiazepines (BZDs) or antiepileptic drugs (AEDs) (Martínez-Rodríguez *et al.*, 2001; Fernández-Torre *et al.*, 2005; Maganti *et al.*, 2006; Thabet *et al.*, 2009).

NCSE is a continuous epileptic condition with no overt tonic, clonic, or tonic-clonic movements. This disorder manifests clinically as altered mental status, with an EEG that is characterised by continuous epileptiform activities (Brenner, 2002; Bearden *et al.*, 2008; Maganti *et al.*, 2008). In general, the administration of BZDs results in an immediate or short-term clinical improvement. However, previous reports have shown that most cases with cephalosporin-related NCSE did not respond to BZD administration; in contrast, these patients gradually recovered consciousness after the withdrawal of cephalosporins (Martínez-Rodríguez *et al.*, 2001; Fernández-Torre *et al.*, 2005; Maganti *et al.*, 2006; Thabet *et al.*, 2009). Despite these findings, the varied responses to BZD administration and the role of BZDs in cephalosporin-related NCSE has rarely been discussed.

In this study, we investigated nine patients suffering from changes in consciousness related to cephalosporin treatment, with generalized periodic discharges (GPDs) on their EEGs. The clinical and EEG manifestations, responses to BZD administration, and the final outcomes are presented for each patient.

Methods

We reviewed the EEG databases of Taipei Veterans General Hospital to identify in-patients who underwent EEG monitoring from September 2009 to December 2011. Among them, those patients who presented with GPDs or GPDs-plus on the EEG were enrolled in the study. The GPDs comprise synchronous and relatively symmetric repetitive waveforms with a relatively uniform morphology and duration (Hirsch *et al.*, 2005), and the intervals between consecutive waveforms are quantifiable and definable. The GPDs-plus comprises superimposed rhythmic or quasi-rhythmic activity of any frequency during the periodic discharges. Two board-certificated neurologists (HYL and HYY) re-read the EEGs of the enrolled patients using referential and differential montages. The EEG recordings were obtained by a minimum of 18 EEG electrodes placed on the patient's scalp according to the international 10-20 system, with at least 30 minutes of recordings.

The medical records of the enrolled cases were then reviewed. All of the enrolled patients exhibited changes in consciousness during the EEG recordings. We selected the patients who had received cephalosporins no earlier than 14 days prior to the onset of change in consciousness, and cephalosporin use was the only identified cause that related to patients' altered consciousness. Those patients with additional factors (other than cephalosporins alone) contributing to their altered consciousness were excluded. Additional management procedures and clinical outcomes were obtained from patients' medical records.

In our cohort, the glomerular filtration rate (GFR) was calculated with the Cockcroft-Gault formula (Cockcroft and Gault, 1976) using the creatinine value obtained on the day of the change in consciousness or the date closest to this event. Acute renal failure was diagnosed when a patient's GFR decreased more than 50% in comparison to his or her baseline GFR, or when a patient required renal replacement therapy due to a worsening of renal function during hospitalisation.

Results

A total of 39 patients with EEG-identified GPDs were enrolled. Fourteen of the patients had received cephalosporins before the onset of changes in consciousness. Among them, five patients were excluded due to additional factors, including severe sepsis and hepatic encephalopathy; a drastically altered electrolyte level or glycaemic alterations may have been linked to their altered status of consciousness. The remaining nine patients (male/female: 4/5; mean age: 72±11.8 years) comprised the final sample in this study (*table 1*). They exhibited changes in consciousness temporally related to the use of cephalosporins, and recovered consciousness after withdrawal of the drug. Six patients had received cefepime and another three patients had received ceftazidime. Laboratory tests and neuroimaging studies (including computed tomography or magnetic resonance imaging) were performed on these patients and could not provide any data to account for their altered consciousness.

Renal function and dosage of cephalosporins

Seven out of nine patients exhibited impaired renal function; four patients had end-stage renal disease with regular dialysis treatment prior to admission, one

Table 1. Demographics, clinical profiles, manifestations, and courses of the nine patients.

Patient	Age (years) /Gender	Renal function	Antibiotic /Treatment duration (days)	Cephalosporins adjusted to renal function?	Clinical manifestations	[a]Onset/ [b]Recovery latencies (days)
1	82/M	GFR 66	Cefepime/7	Yes	Convulsions, drowsiness	6/1
2	62/F	ARF, no dialysis, GFR 15	Cefepime/7	No	Confusion, slowed response time	6/2
3	81/M	GFR 60	Cefepime/13	Yes	Drowsiness	4/4
4	50/F	ESRD s/p HD	Ceftazidime/8	No	Myoclonus, confusion	8/2
5	65/M	ARF s/p HD	Cefepime/10	No	Irritability, confusion	5/2
6	65/F	ESRD s/p HD	Cefepime/4	No	Irritability, confusion	3/3
7	81/F	GFR 45	Cefepime/4	No	Convulsions, drowsiness, myoclonus	2/4
8	83/M	ESRD s/p CAPD	Ceftazidime/7	Yes	Lethargy followed by confusion and myoclonus	3/2
9	79/F	ESRD s/p HD	Ceftazidime/8	No	Irritability, confusion, myoclonus	7/4

GFR: glomerular filtration rate; ARF: acute renal failure; ESRD: end-stage renal disease; HD: hemodialysis; CAPD: continuous ambulatory peritoneal dialysis.
[a]Onset latency refers to the time from cephalosporin administration to an observable change in consciousness;
[b]Recovery latency refers to the time from cephalosporin withdrawal to recovery of consciousness.

patient had chronic kidney disease without dialysis treatment, and two patients suffered from acute renal failure during admission while one of them received haemodialysis treatment. Only one of the patients with impaired renal function received an adjusted dose of cephalosporins for his GFR, whereas the other six patients received unadjusted or inadequately adjusted doses of cephalosporins (*table 1*).

Manifestations of cephalosporin-related changes in consciousness

Acute and subacute changes in consciousness were reported for all of the patients. The mean time between cephalosporin administration and the observed changes in consciousness was 4.9±2.0 days (range: 2-8 days). The patients' symptoms included lethargy, slow response, confusion, amnesia, incoherent speech, psychomotor agitation, drowsiness, and myoclonus. Two of the patients had generalized tonic-clonic seizures followed by prolonged drowsiness.

Clinical course and clinical response to BZD administration

After the EEGs were obtained, cephalosporins were withdrawn for all of the patients, except for Patient 3. Patient 3 continued receiving cephalosporins because it was not initially considered the cause for his change in consciousness. He was treated for NCSE with repetitive intravenous boluses of midazolam, followed by a continuous midazolam drip and levetiracetam use, but neither his EEG nor his clinical condition improved. Cephalosporins were discontinued on the ninth day since the change of consciousness, and his EEG then improved dramatically. He regained a baseline level of consciousness four days later.

Of the other eight patients, seven received intravenous BZDs, three received concomitant AEDs, and one patient did not receive BZDs or AEDs (*table 2*). Patient 2 responded to BZD treatment immediately. She became alert and was able to respond to her name and recognise her family after receiving 2 mg of

Table 2. EEG characteristics, treatments, and clinical and EEG responses to BZDs of the nine patients.

Patient	EEG characteristics during state of altered consciousness/upon recovery of consciousness	BZDs/dosage (the interval between BZD administration and the last dose of cephalosporins)	Clinical response/EEG response to BZD administration	AEDs
1	Diffuse sharp waves in quasi-periodic pattern at 1.5-2 Hz, FIRDA, DBS: 4-5 Hz / FIRDA, DBS: 7-8 Hz	None	None / None	None
2	Diffuse periodic sharp interval high-voltage diffuse discharges at 2 Hz, DBS: 4-6 Hz / FIRDA, DBS: 7 Hz	Lorazepam / 2 mg (39 hours), 2 mg (44 hours)	Transiently orientated to the first dose, and recovery of consciousness to the second dose / none	Valproic acid
3	Bisynchronous short-interval epileptiform discharges at 1.5-2 Hz, spikes over left frontal and right parieto-occipital regions, DBS: 3-4 Hz / DBS: 5-7 Hz	Midazolam / 5 mg repetitive injections followed by a continuous drip (cephalosporin was not stopped)	No improvement / no change	Levetiracetam
4	Diffuse intermittent triphasic waves with spiky wave features on the initial phase, FIRDA, DBS: 5-6 Hz / FIRDA, DBS: 7 Hz	Lorazepam / 2 mg (4 hours)	No improvement / none	None
5	Diffuse periodic sharp interval diffuse discharges at 2 Hz with maximal amplitude shifting between anterior and posterior head regions, DBS: 4-6 Hz / FIRDA, DBS: 7 Hz	Midazolam / 5 mg (1 hour), 2.5 mg (25 hours)[a]	Transiently responsive to the second dose / sharp waves briefly attenuated	Oxcarbazepine
6	Intermittent diffuse high-voltage sharply contour components in the triphasic waves at 1.5-2 Hz, DBS: 5 Hz / FIRDA, DBS: 7 Hz	Midazolam / 5 mg (28 hours)[a]	No improvement / no change	None
7	Periodic short interval diffuse discharges at 3-4 Hz with maximal amplitude at anterior quadrant and left parieto-occipital regions, DBS: 5 Hz / none	Midazolam / 5 mg (3 hours), 5 mg (7 hours), 5 mg (10 hours)[a]	No improvement / no change	Valproic acid
8	Diffuse sharp waves in quasi-periodic patter at 2-2.5 Hz, FIRDA, DBS: 4-6 Hz / none	Lorazepam / 2 mg (24 hours)[a]	No improvement / sharp waves attenuated	None
9	Generalized periodic epileptiform discharges separated by interval of 0.5-1s, DBS: 5-6 Hz / DBS: 6 Hz, FIRDA	Lorazepam / 2 mg (60 hours)[a]	No improvement / epileptiform discharges attenuated	None

FIRDA: frontal intermittent rhythmic delta activity; DBS: diffuse background slowing; BZD: benzodiazepine; AED: antiepileptic drug.
[a]BZD administered during EEG recordings.

intravenous lorazepam (the last dose of cephalosporin was given 39 hours beforehand). However, she soon fell asleep and returned to a state of confusion until five hours later, when another injection of lorazepam caused her to regain consciousness. Patient 5 received 5 mg of midazolam intravenously one hour after his last dose of cephalosporin, however, he did not show any improvement with regards to consciousness. He received regular haemodialysis later in the day, and the next morning, he was monitored by video-EEG, which indicated that the interval between two subsequent sharp waves was greater (*figure 1A*) than that observed on his first EEG 24 hours before (data not shown). A second intravenous injection of midazolam during video-EEG attenuated the high-voltage sharp waves (*figure 1B*), and the patient became transiently responsive. However, he quickly returned to a drowsy state, and sharp waves also returned on the subsequent EEG recording.

A total of seven doses of BZDs were injected into another five patients, after a mean of 18.9 hours (range: 3-60 hours) after the last dose of cephalosporins. None of these patients improved clinically after BZD administration, but they gradually regained consciousness within two to four days after cephalosporins were discontinued. The only patient (Patient 1) who did not receive BZDs or AEDs during his hospital stay gradually recovered consciousness one day after the withdrawal of cephalosporins. In the end, all of the nine patients regained consciousness, and the mean time between the last dose of cephalosporins and the recovery of consciousness was 2.7±1.1 days (range: 1-4 days).

EEG findings and EEG responses to BZD administration

The EEG findings were similar among all of the patients, which were characterised as GPDs or GPDs-plus superimposed on diffuse background slowing (DBS) (*table 2*, *figure 2*). BZDs were administered during EEG recordings in five of the patients. In three of them, the GPDs were reduced or completely eliminated within three to five minutes after BZD administration, however, only one patient displayed simultaneous clinical improvement. The generalized sharp waves in another two patients remained unchanged with BZD administration (*table 2*). Seven of the patients had follow-up EEGs after they regained consciousness, and all of these showed that the GPDs had subsided.

Discussion

We identified nine patients with cephalosporin-related changes in consciousness and EEGs showing GPDs. Seven of the patients exhibited impaired renal function, and six of them did not receive adjusted doses of cephalosporins. One of the patients received repetitive BZD injections without discontinuing cephalosporin treatment, and neither his clinical symptoms nor GPDs on EEG responded to BZDs. Seven of the patients were treated with BZDs after discontinuation of cephalosporins, but only two of them showed immediate clinical improvements with BZD administration. One of the patients did not receive BZDs or AEDs, and this patient spontaneously recovered consciousness soon after cephalosporins were discontinued. The changes in consciousness were reversible in all of the nine patients.

Cephalosporins have been shown to block the gamma-aminobutyric acid (GABA)-A receptor in the central nervous system (Curtis *et al*., 1972; Sugimoto *et al*., 2003). GABA is the primary inhibitory neurotransmitter in the central nervous system. Therefore, a higher level of cephalosporins, presenting a stronger GABA antagonist effect, may lead to neuronal excitability that may manifest as epileptic discharges. In addition, cephalosporins can increase cytokines in brain tissues (Alkharfy *et al*., 2000), which may injure neurons and result in encephalopathy. The altered permeability of the blood-brain barrier in patients with impaired renal function, as well as the accumulated doses of cephalosporins due to the patients' impaired eliminated route, increase the concentration of cephalosporins and toxic organic acid compounds in their brain tissues (Schliamser *et al*., 1991). Therefore, patients with impaired renal function have a higher risk of developing seizure and encephalopathy when receiving cephalosporins.

BZDs are the first line of treatment for controlling status epilepticus. BZDs bind to the allosteric binding site on the GABA-A receptor and increase the affinity of GABA for its receptor (Möhler and Okada, 1977). Generally, BZD administration rapidly reverses the altered mental status presenting in NCSE. The inconsistent responses to BZDs in our patients with cephalosporin-related GPDs may be explained based on two possibilities. First, the amount of cephalosporins in a patient's brain tissue may determine the competitiveness of BZDs on GABA-A receptors. This may explain why Patient 5 did not respond to the first dose of BZD given just one hour after his last dose of cephalosporin, but he responded to the second dose of BZD 24 hours later when the amount of cephalosporin should have been decreased with time and haemodialysis. However, this could not be demonstrated since we did not measure the level of cephalosporins in the patients' CSF or brain tissues. Second, NCSE might not be the only factor contributing to the patients' impaired consciousness. Short-interval GPDs may occur in toxic-metabolic

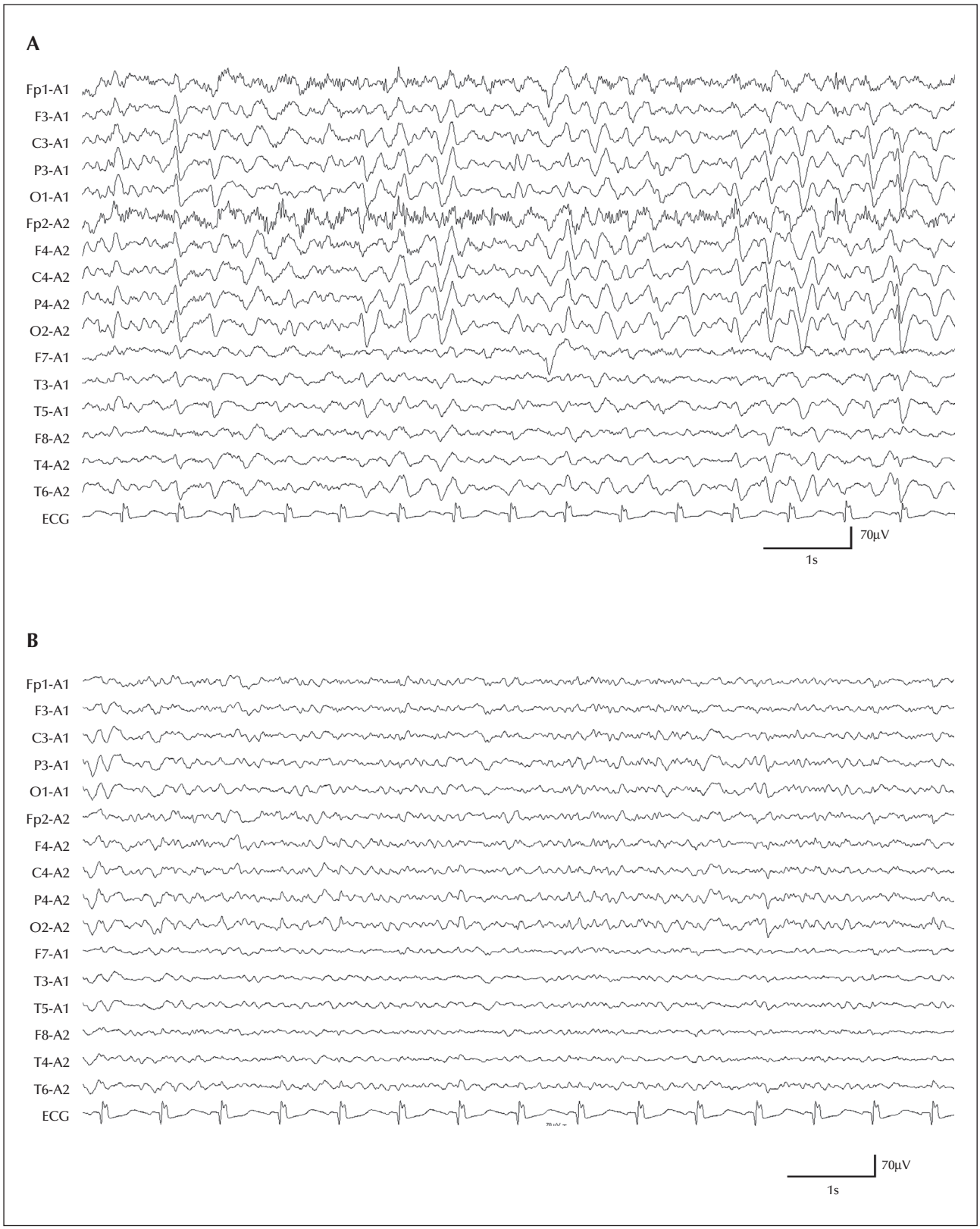

Figure 1. The EEG of Patient 5 before and after BZD injection (A) Periodic sharp waves with prolonged intervals of inter-sharp waves (B) Sharp waves were attenuated 100 seconds after BZD injection.

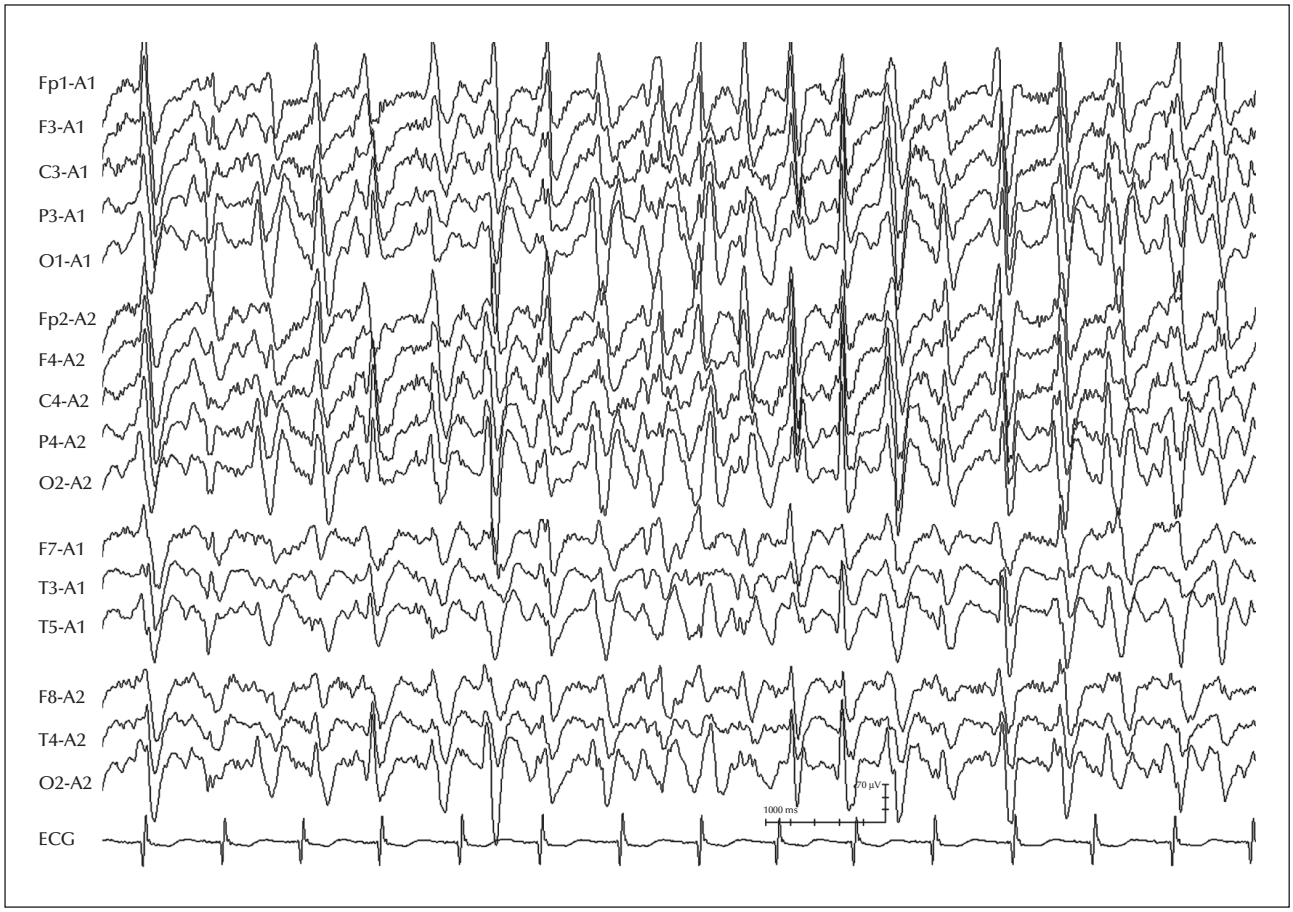

Figure 2. The EEG of Patient 2 showed GPDs-plus The EEG shows symmetric and synchronous periodic sharp waves at 2-3 Hz, with a preceding and a following positive phase, which exhibits triphasic morphology in a rhythmic pattern.

encephalopathies, anoxic brain injury, Creutzfeldt-Jakob disease, and NCSE (Husain *et al*., 1999; Yemisci *et al*., 2003; Korabathina and Benbadis, 2007; Andraus *et al*., 2012), hence, it is challenging to distinguish between the aetiology of GPDs as either epileptic or toxic-metabolic. The diagnosis of NCSE is primarily dependent on EEG because of its non-specific and pleomorphic clinical presentations (Brenner, 2002; Bearden *et al*., 2008). However, the EEG takes several forms, including those that clearly denote NCSE and those which are less easy to be interpreted and probably denote NCSE only in some cases (Walker *et al*., 2005). GPDs in patients whose EEGs showed no previous similar abnormalities have been proposed as one of the EEG patterns that belong to the equivocal EEG criteria for diagnosing NCSE (Walker *et al*., 2005). In fact, a controversial aspect of NCSE is the suggestion that it represents a "boundary syndrome", in which it is unclear whether the extent of EEG activity results from the symptoms observed or whether it is simply the result of underlying cerebral dysfunction (Walker *et al*., 2005; Shorvon, 2007; Sutter and Kaplan, 2012). Drug-induced epileptic encephalopathy, confusional states, or even coma, with non-evolving epileptiform EEG pattern, are some of the clinical situations that are most likely to occur in boundary syndromes (Sutter and Kaplan, 2012). Therefore, we suggest that GPDs induced by cephalosporins in our patients may have exhibited epileptic, encephalopathic, or both features in varying degrees, and the reversal of the epileptogenic effect, but not the encephalopathic effect, of cephalosporins was not enough to bring the patients back to clear consciousness. This may explain why some of the patients did not respond to BZD injections regarding both clinical and EEG aspects. In addition, it should be noted that the sharp waves associated with metabolic encephalopathy can also be suppressed by BZDs, as is the case in NCSE (Fountain and Waldman, 2001). To sum up, for patients with cephalosporin-related GPDs, who do not respond to BZDs clinically, encephalopathy should be considered as a possible underlying aetiology, while on-going seizure should also not be ruled out.

Previous reports regarding cephalosporin-related NCSE or encephalopathy have also shown inconsistent responses to BZD injections. Martínez-Rodríguez *et al*.

reported 10 patients diagnosed with cephalosporin-related NCSE (Martínez-Rodríguez *et al*., 2001), whose EEG showed generalized sharp waves or sharp and slow waves. Seven of the patients received intravenous clonazepam, but only two responded to the treatment immediately. The remaining five patients and the other three who did not receive BZDs gradually recovered consciousness within two to seven days after discontinuing cephalosporins. Similarly, another study reported by Fernandez-Torre *et al*. showed that patients with cephalosporin-induced NCSE responded to BZD treatment inconsistently, and the EEGs of these patients were characterised as generalized rhythmic sharp waves (Fernández-Torre *et al*., 2005). Another case series with a total of 19 patients was reported by P. Jallon *et al*. as cefepime-related encephalopathy. The patients' EEGs showed bilateral rhythmic triphasic sharp-wave activities, with a high-voltage positive phase that was preceded and followed by a lower-amplitude negative wave (Jallon *et al*., 2000). Three of the patients received BZD injections, but none of them responded to the treatment. All of the 19 patients improved 24-48 hours after the discontinuation of cefepime. Overall, taking into consideration the above-mentioned studies and the present study, withdrawal of the offending drug is mandatory in treating these patients. In some cases with impaired renal function, haemodialysis may be necessary as part of the treatment. Although BZD injections did not result in promising clinical improvement, the clinical value of BZD administration should not be underestimated since a positive response to BZDs assists the diagnosis of NCSE. Of note, we did not study the patients whose EEG did not show GPDs or GPDs-plus, and their responses to BZDs are unknown. A recent study reported that responses to acute intravenous BZDs are predictive of subsequent prognosis in patients with suspected NCSE (Hopp *et al*., 2011). However, cephalosporin-affected NCSE was not specified in that study, thus further investigations are needed to verify whether responses to BZDs can also predict outcome in these patients.

The EEG patterns in critically ill patients are variable. There is no consensus regarding which patterns require treatments or how aggressive the treatments should be (Chong and Hirsch, 2005). In spite of the effort to unify classification and nomenclature of the EEG patterns by the American Clinical Neurophysiology Society, there was certain interrater disagreement (Gerber *et al*., 2008). Therefore, the EEG patterns of our patients may be interpreted differently by another EEG reader. It should also be noted that in some cases, it is difficult to define patterns of EEG as periodic or rhythmic, since one may overlap another, and the intervals between consecutive waves may be less quantifiable when the frequency of discharges is high.

In conclusion, withdrawal of neurotoxic antibiotics is mandatory for treating patients with cephalosporin-related GPDs. BZD administration does not result in promising clinical improvements in most of the patients, but can assist the diagnosis of NCSE in responding patients. Further prospective, randomised, controlled, double-blind studies are necessary to elucidate whether BZDs or AEDs are beneficial to clinical outcomes in patients with cephalosporin-related GPDs. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

We thank Miss CW Lu, Miss HT Wang, Miss YJ Chou, Miss PS Shao and Miss JF Meng for their assistance in data collection. This study was supported by a grant from the Taipei Veterans General Hospital (V102C-193).

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

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TEST YOURSELF

(1) What are the possible mechanisms underlying cephalosporin-related seizures and encephalopathy?

(2) Why do patients with impaired renal function have a higher risk of cephalosporin-related seizures and encephalopathy?

(3) Based on this study and previous reports, can BZD injections always immediately reverse the altered state of consciousness in patients with cephalosporin-related GPDs?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".