Clinical commentary

Epileptic Disord 2020; 22 (6): 828-33

A case series of super-refractory status epilepticus successfully treated with electroconvulsive therapy

Hui Jan Tan [1], Tze Yuan Tee [1], Mazlina Husin [1], Ching Soong Khoo [1], Luke Sy-Cherng Woon [2]

[1] Neurology Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia
[2] Department of Psychiatry, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Received March 21, 2020; Accepted August 27, 2020

ABSTRACT – Super-refractory status epilepticus (SRSE) is a neurocritical emergency, associated with significant morbidity and mortality. The precise pathophysiology is still not completely understood. The likelihood of spontaneous seizure termination reduces with time, and it is of paramount importance to abort status in order to prevent permanent long-term neurological sequelae and death. A few neuroprotective strategies, such as general anaesthesia, steroids, ketogenic diet and hypothermia, have been used to treat SRSE, however, the clinical outcome remains inconclusive. We herein present two cases of SRSE, which were successfully treated with electroconvulsive therapy (ECT) after failing all pharmacological measures.

Key words: status epilepticus, epilepsy, electroconvulsive therapy

Refractory status epilepticus (RSE) is defined as status epilepticus (SE) that persists despite optimal dosage of two intravenous antiepileptic drugs (AEDs), one of which is a benzodiazepine (Rossetti and Lowenstein, 2011). Super-refractory SE (SRSE) is defined as SE that persists for 24 hours or more after the use of anaesthetic therapy, including cases that recur upon reduction or withdrawal of anaesthesia (Shorvon and Ferlisi, 2011). RSE and SRSE are estimated to occur in 12-43% and 15-20% of cases of SE, respectively (Shorvon and Ferlisi, 2011; Kantanen *et al*., 2015). To date, evidence-based therapeutic strategies for SRSE are sparse. Electroconvulsive therapy (ECT) has been applied in a number of cases of (S)RSE with success (Lambrecq *et al*., 2012; Ahmed *et al*., 2018), although its exact mechanism in terminating status is still unclear. Two cases of SRSE from our tertiary centre, treated successfully with ECT, are detailed in this report.

Correspondence:
Ching Soong Khoo
Neurology Unit,
Department of Medicine,
Universiti Kebangsaan Malaysia Medical Centre,
Jalan Yaacob Latif,
Bandar Tun Razak, Cheras,
56000 Kuala Lumpur, Malaysia
<chingsoongkhoo@gmail.com>

doi:10.1684/epd.2020.1233

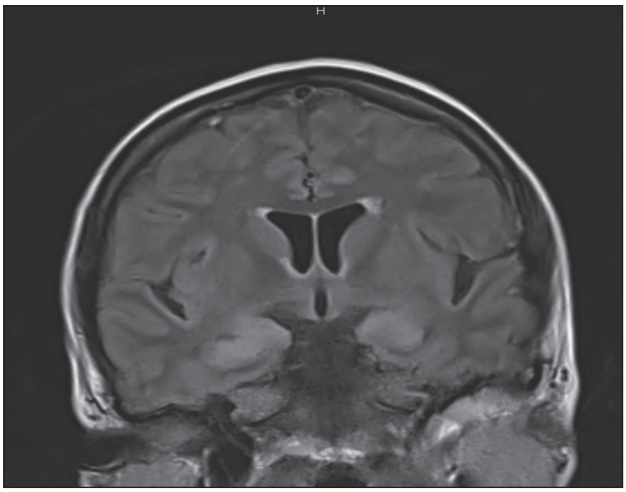

Figure 1. Brain MRI (T2 FLAIR sequence) reveals hyperintensity in both temporal lobes.

Case 1

A 42-year-old Indonesian woman with underlying human immunodeficiency virus infection presented with a four-day history of fever, reduced consciousness and multiple episodes of generalized tonic-clonic seizures. She was intubated for SE and commenced on midazolam infusion. Her cerebrospinal fluid (CSF) showed mildly elevated protein at 424 mg/dL and lymphocytosis with normal CSF to serum glucose ratio. Her CSF was negative for herpes simplex virus 1 and 2 (HSV-1 and HSV-2), Epstein-Barr virus (EBV), cytomegalovirus (CMV), Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae and Listeria monocytogenes. Both her serum and CSF were also negative for anti-NMDAR, anti-AMPA 1/2, anti-CASPR2, anti-LGI1, anti-DPPX and anti-GABA B antibodies. Brain magnetic resonance imaging (MRI) showed high signal intensity on T2 FLAIR sequence in both temporal regions (*figure 1*). Her electroencephalogram (EEG) showed (*figure 2*) sharp waves arising from bilateral frontal regions. She was treated for herpes simplex encephalitis with intravenous acyclovir for 21 days given the MRI findings. On the fifth day of admission, she developed frequent myoclonic jerks, which were particularly stimulus-sensitive. Generalised myoclonic seizures (possibly due to hypoxic encephalopathy) persisted despite optimal doses of sodium valproate, phenytoin, levetiracetam and clonazepam. Methylprednisolone was administered for possible autoimmune encephalitis. Other immunomodulatory agents were not attempted owing to financial constraints. Anaesthetic drugs such as midazolam, propofol and thiopentone were futile in aborting her status. After a multidisciplinary discussion, we decided to resort to ECT. The patient underwent a total of eight ECT sessions by the second week of admission. The ECT machine used was the MECTA spECTrum 5000Q device (MECTA Corp, Tualatin, Oregon). In the first ECT session, she was subjected to a frequency of 50 Hz, pulse width of 0.5 msec, current of 800 mA and charge of 156 mC. The current was delivered via bilateral temporal areas. For the consecutive daily ECT sessions, the charge was gradually increased to 208 mC, 312 mC, 352 mC, 384 mC and later 416 mC. All AEDs and anaesthetic agents were maintained throughout the ECT trials. Clinical improvement was observed gradually within two weeks after the ECT, during which the frequency of myoclonus reduced and anaesthetic agents were tapered off. About six weeks after ECT, her tracheostomy was removed and she was discharged home with only low doses of phenobarbitone and clonazepam. Her Glasgow Outcome Scale (GOS) was 4. She did not return to the clinic for follow-up.

Case 2

A previously healthy 36-year-old man presented with a five-day history of fever, which was associated with altered behaviour for one day. He was intubated on arrival for generalized convulsive SE. His CSF analysis, viral screening and brain MRI were unremarkable. Connective tissue screening and work-up for autoimmune encephalitis, including anti-NMDAR, anti-AMPA 1/2, anti-CASPR2, anti-LGI1, anti-DPPX and anti-GABA B antibodies, were negative. He was treated for viral meningoencephalitis with acyclovir. His seizures remained refractory despite multiple AEDs (sodium valproate, phenytoin, levetiracetam, lacosamide, carbamazepine, perampanel and clonazepam). By the second week, he was given a course of methylprednisolone, followed by intravenous immunoglobulin (IVIg) for probable autoimmune encephalitis. Midazolam, propofol and thiopentone could not terminate his seizures clinically and electrographically. Lateralized periodic discharges (LPDs) from the right hemisphere, while he was at the intensive care unit, are presented in *figure 3*. By the second week, he was subjected to bilateral ECT, and a total of eight sessions on consecutive days were delivered to him. For the first ECT session, he was subjected to a frequency of 50 Hz, pulse width of 0.5 msec, current of 800 mA and charge of 300 mC. The charge was increased gradually to 420 mC, 512 mC, 614 mC and later 768 mC. During the ECT trials, all AEDs and anaesthetic agents were maintained. Motor seizures resolved two weeks after the ECT. He was discharged with tracheostomy after five months of hospitalization. Upon discharge, his eye component (E) was 4 and motor component (M) was 6. His seizures

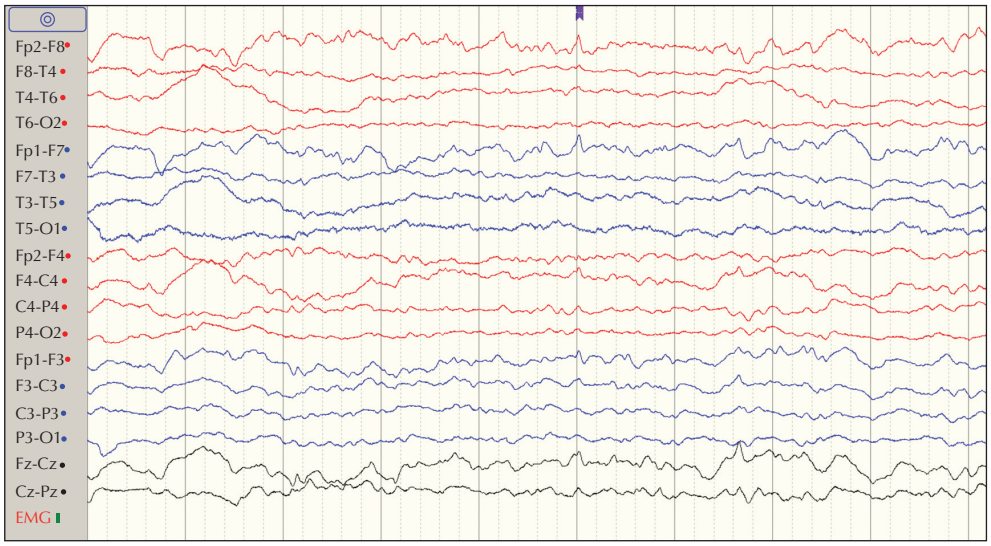

Figure 2. EEG shows sharp waves from bilateral frontal regions.

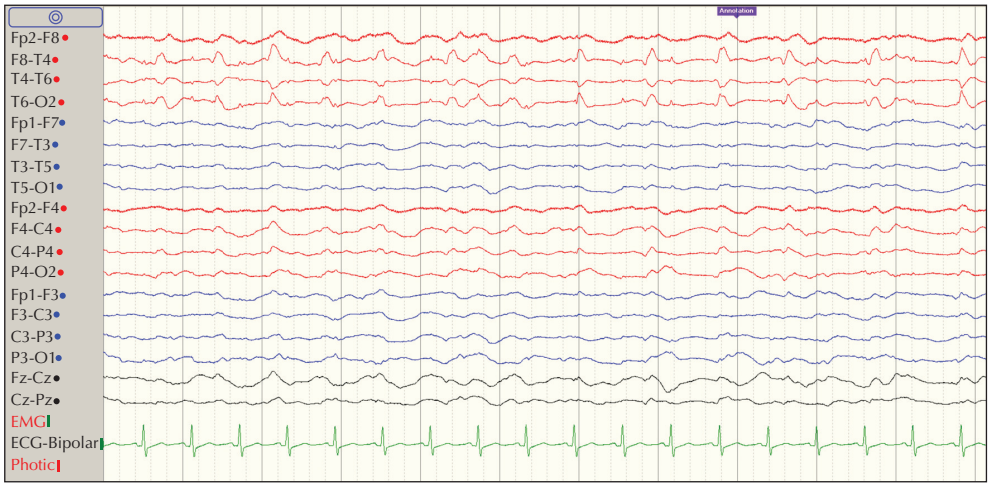

Figure 3. EEG reveals periodic discharges in the right hemisphere.

were controlled with perampanel. *Table 1* summarizes the ECT regimes and outcome of both cases.

Discussion

Benzodiazepines such as lorazepam or diazepam are the initial treatment for early SE. Intravenous AEDs such as fosphenytoin, valproate or levetiracetam are added if seizures persist. When patients progress to RSE, general anaesthesia (thiopental, midazolam or propofol) is subsequently introduced, which is usually adequate to control the seizures (Shorvon and Ferlisi, 2011). One of the most crucial factors that predicts the outcome of SE is the aetiology of status. Age and underlying medical conditions are also important prognostic factors in SE (Rossetti and Lowenstein, 2011; Alvarez *et al.*, 2012). Novy *et al.* showed that 21% of the patients with RSE would return to their baseline clinical status, compared to 63% of those with non-RSE (Novy *et al.*, 2010). The mortality rate of SRSE ranges between 30 and 50% (Shorvon and Ferlisi, 2011). Regarding a study on the long-term outcome of both SRSE and RSE by Ferlisi and Shorvon (2012), (35)% of the patients did not survive, about a third survived with neurological deficits, and the remaining third returned to their baseline condition. It is thus crucial to terminate seizures as quickly as possible in order to prevent any further neuronal damage. A few anecdotal reports have described the usage of other pharmacological agents, such as isoflurane, ketamine, lidocaine, verapamil and steroids, in managing RSE (Rossetti and Lowenstein,

Table 1. Summary of our two cases treated with ECT.

	Case 1	Case 2
Age (years)/ Sex	42/ Female	36/ Male
Aetiology of SE	Probable HSV encephalitis	Probable autoimmune encephalitis
Type of SE	Generalized convulsive; later became generalized myoclonic	Generalized convulsive
EEG	Bi-frontal sharp waves	LPDs
Brain MRI	Hyperintensity in both temporal lobes	Normal
Comorbidities	HIV	None
Known case of epilepsy	No	No
AEDs prior to ECT	Sodium valproate, phenytoin, levetiracetam, clonazepam, phenobarbitone	Sodium valproate, phenytoin, levetiracetam, lacosamide, carbamazepine, perampanel, clonazepam
Days till ECT trial	10	9
Electrode positioning	Bitemporal	Bitemporal
ECT sessions	8 sessions in 5 days	8 sessions in 8 days
ECT regime	Day 1: 1st session: charge 156 mC, clinical seizure 24 s Day 2: 2nd session: charge 156 mC, clinical seizure 25 s 3rd session: charge 156 mC, clinical seizure 12 s Day 3: 4th session: frequency 40 Hz, charge 208 mC, clinical seizure nil 5th session: frequency 50 Hz, charge 312 mC, clinical seizure 10 s Day 4: 6th session: frequency 80 Hz, charge 352 mC, clinical seizure 14 s 7th session: charge 384 mC, clinical seizure 11 s Day 5: 8th session: charge 416 mC, clinical seizure 14 s	Day 1: 1st session (1st attempt): charge 300 mC, clinical seizure nil 2nd attempt: frequency 70 Hz, charge 412 mC, clinical seizure nil Day 2: 2nd session: frequency 80 Hz, charge 512 mC, clinical seizure 17 s Day 3: 3rd session: charge 512 mC, clinical seizure 22 s Day 4: 4th session: charge 512 mC, clinical seizure 15 s Day 5: 5th session: charge 614 mC, clinical seizure 20 s Day 6: 6th session: charge 614 mC, clinical seizure 20 s Day 7: 7th session: charge 614 mC, clinical seizure 18 s Day 8: 8th session: frequency 120 Hz, charge 768 mC, clinical seizure 20 s
Duration of response	Reduced myoclonic jerks in 2 weeks after the ECT	Focal jerky movements resolved about 2 weeks after the ECT
Adverse effects of ECT	None	None
Outcome	Myoclonus was controlled with low doses of phenobarbitone and clonazepam; tracheostomy was removed; GOS 4/5	Discharged with tracheostomy after 5 months of hospitalization. E4M6. Seizures were controlled with perampanel.

ECT: electroconvulsive therapy; SE: status epilepticus; EEG: electroencephalogram; MRI: magnetic resonance imaging; AEDs: antiepileptic drugs; HSV: herpes simplex virus; HIV: human immunodeficiency virus; LPDs: lateralized periodic discharges; GOS: Glasgow Outcome Scale.

2011). In some cases, non-pharmacological management such as resective neurosurgery, acute vagal nerve stimulation implantation, transcranial magnetic stimulation and brain hypothermia have been attempted to treat RSE (Rossetti and Lowenstein, 2011).

The usage of ECT in SE has been reported in case reports since the 1990s (Lambrecq *et al*., 2012). The exact mechanism of ECT as an anticonvulsant remains elusive (Rossetti and Lowenstein, 2011; Schneegans *et al*., 2019). The use of ECT as a treatment option for SE is also seen in paediatric groups after conventional therapy fails (Incecik *et al*., 2015; Ray, 2017). It is hypothesized that the anticonvulsant properties of ECT are due to direct or indirect neurotransmitter alteration that reduces normal neuronal activities, namely seizure duration, seizure threshold, ictal and immediate postictal seizure expression, cerebral blood flow and metabolism of glucose, and EEG slow-wave activity (Sackeim, 1999). ECT is believed to enhance presynaptic release and transmission of γ -aminobutyric acid (GABA), hence the refractory period is lengthened by suppression of the neural metabolic activity after a seizure. ECT also affects the ratio of inhibitory to excitatory stimulus (Sackeim *et al*., 1983). Other probable anticonvulsant activities are enhancement of inhibitory neuropeptides such as neuropeptide-Y, somatostatin and endothelin, achieving burst suppression, and forming long-term neuronal plasticity and anti-kindling action that results in neuronal loss (Ray, 2017). Before administering ECT, anaesthetic agents should be reversed and AEDs weaned. These agents reduce cortical excitability, preventing a formed convulsion by ECT, thus preventing effective ECT (Shorvon and Ferlisi, 2011).

Based on a literature review by Lambrecq *et al*. in 2012, ECT was shown to prevent SE in 80% of the 11 cases, even though only three patients (27%) managed to recover with full functions (Lambrecq *et al*., 2012). On average, these patients underwent ECT between 30 to 40 days after the onset of SE. However, almost half of the case reports did not mention the intensity of charges during ECT. Furthermore, the design of the ECT sessions (total number of sessions and number of seizure inductions per session) and placement of the electrodes also varied. These key factors are believed to have a bearing on the efficacy of ECT and patients' outcome.

A systematic review on 14 original papers by Zeiler *et al*. suggested a potential impact of ECT on controlling seizures in RSE. However, given the wide heterogeneity of the retrospective data, including aetiology, seizure types of RSE, various ECT regimes and parameters, the routine use of ECT cannot be recommended for seizure control in cases of RSE (Zeiler *et al*., 2016). San-Juan *et al*. reported an 80% disruption rate of SE due to ECT with adverse events in 5%, based on a review paper on various neuromodulation techniques (San-Juan *et al*., 2019).

Schneegans *et al*. (2019) were in favour of stimulation charges of high intensity (mean output charge of 1031 mC) compared to those reported by Kamel *et al*. (2010) and Ahmed *et al*. (2018) with a mean of 507 mC and 504 mC, respectively. With this intensified stimulus setting and daily treatment sessions, adequate induction of seizures was achieved with postictal suppression. However, there has been no standardized regime, which could confirm the most effective parameters used to terminate status.

Conclusion

Our case series suggests that ECT may have a role in terminating status after exhausting all pharmacological measures. Larger prospective unbiased trials are required to yield more robust evidence in order to understand the role and benefits of ECT, and subsequently design a standardized regime of ECT for SRSE. □

Disclosures.
None of the authors have any conflict of interest to declare.

References

Ahmed J, Metrick M, Gilbert A, *et al*. Electroconvulsive therapy for super refractory status epilepticus. *J Ect* 2018; 34: e5-9.

Alvarez V, Januel JM, Burnand B, Rossetti O. Role of comorbidities in outcome prediction after status epilepticus. *Epilepsia* 2012; 53: e89-92.

Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain* 2012; 135: 2314-28.

Incecik F, Horoz OO, Herguner OM, Yıldızdas D, Altunbasak S. Electroconvulsive therapy for refractory status epilepticus in a child: a case report. *Ann Indian Acad Neurol* 2015; 18: 364-5.

Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA. Electroconvulsive therapy for refractory status epilepticus: a case series. *Neurocrit Care* 2010; 12: 204-10.

Kantanen AM, Reinikainen M, Parviainen M, *et al*. Incidence and mortality of super-refractory status epilepticus in adults. *Epilepsy Behav* 2015; 49: 131-4.

Lambrecq V, Villega F, Marchal C, *et al*. Refractory status epilepticus: electroconvulsive therapy as a possible therapeutic strategy. *Seizure* 2012; 21: 661-4.

Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010; 51: 251-6.

Ray A. Treatment of refractory status epilepticus with electroconvulsive therapy: need for future clinical studies. *Int J Epilepsy* 2017: 98-103.

Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. *Lancet Neurol* 2011; 10: 922-30.

Sackeim HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. *J Ect* 1999; 15: 5-26.

Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR. Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. *Biol Psychiatry* 1983; 18: 1301-10.

San-Juan D, Dávila-Rodríguez DO, Jiménez CR, *et al*. Neuromodulation techniques for status epilepticus: a review. *Brain Stimul* 2019; 12: 835-44.

Schneegans H, Stetefeld H, Dohmen C, Onur OA, Lehnhardt FG. Successful treatment of super-refractory status epilepticus with high-intensity electroconvulsive therapy - a case report and review of the current literature. *J Epilepsy Res* 2019; 9: 76-82.

Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011; 134: 2802-18.

Zeiler FA, Matuszczak M, Teitelbaum J, Gillman LM, Kazina CJ. Electroconvulsive therapy for refractory status epilepticus: a systematic review. *Seizure* 2016; 35: 23-32.

TEST YOURSELF

(1) What are the proposed key factors that may affect the outcome of the SRSE patients treated with ECT?

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".