Electroconvulsive therapy for new-onset super-refractory status epilepticus

Eric LY Chan *, MB, BS, FRCP, **WC Lee,** MB, BS, FHKAM (Medicine), **CK Koo,** MB, BS, FHKCA, **Horace ST King,** BNHS, FPHKAN, **CT Woo,** FPHKAN, **SH Ng,** MB, BS, FHKAM (Medicine)

Department of Medicine and Geriatrics, Tuen Mun Hospital, Tuen Mun, Hong Kong

* Corresponding author: chanlye@ha.org.hk

Hong Kong Med J 2018;24:307–10
DOI: 10.12809/hkmj154501

Introduction

Despite the advances in neuroscience and medical therapy for epilepsy, status epilepticus, especially when refractory or super-refractory (defined as seizure that continues or recurs ≥24 hours after onset of anaesthetic therapy, including cases that recur on reduction or withdrawal of anaesthesia),[1] remains an enormous challenge. Multiple and high-dose drug loading is usually prescribed but may be futile. New modalities of treatment including hypothermia and ketogenic diets have been tried with some success in reported case series.[2] We report a case of new-onset super-refractory status epilepticus treated successfully with electroconvulsive therapy (ECT).

Case presentation

A 31-year-old male with a history of childhood asthma presented to Tuen Mun Hospital in November 2012 following onset of generalised tonic-clonic seizure at home. He had upper respiratory symptoms with fever, myalgia, and cough for a week previously. There was no history of recent travel or drug abuse.

Physical examination revealed no focal neurological abnormalities. Investigations showed a normal routine blood picture and renal function except mild liver impairment with alanine aminotransferase level of 72 U/L. General autoimmune (antinuclear antibodies, anti–early nuclear antigen antibodies, C3/C4 and antithyroid antibodies) and toxicology screening were negative. Dried blood spot test for neurometabolic screening was also negative. Examination of cerebrospinal fluid showed white blood cell count 9 per mm^3, red blood cell 2 per mm^3, protein 0.54 g/dL, and glucose 5.4 g/dL. Microbiological investigations (herpes simplex virus, human immunodeficiency virus, Japanese encephalitis virus, varicella zoster virus, and enteroviruses) were negative. Serology for neurosyphilis and leptospirosis was also negative. Serum anti-CASPR2 Ab, anti-LGI1 Ab, anti-VGKC Ab, and anti-NMDAR Ab (serum and cerebrospinal fluid) were all negative.

He was initially treated with intravenous acyclovir and ceftriaxone for presumed acute infectious meningoencephalitis. Routine electroencephalogram (EEG) showed a generalised slow background of 4 to 6 Hz without epileptiform discharges. He developed a clustering of generalised tonic-clonic seizures 2 days later and was admitted to the intensive care unit. He underwent mechanical ventilation and aggressive treatment with medication at the maximal tolerable dosage including intravenous phenytoin (300 mg/d), valproate (1200 mg/d), midazolam (~60 mg/h), propofol (up to 110 mg/h), phenobarbitone (300 mg/d), and levetiracetam (3000 mg/d). Despite treatment he remained convulsive with seizures evident on EEG. Intravenous immunoglobulin was first given 8 days following admission for possible autoimmune encephalitis but was unsuccessful. Electroencephalogram showed generalised epileptiform discharges and runs of EEG seizure activity over the bitemporal and bifrontocentral regions. His condition was later complicated by rhabdomyolysis and renal failure (creatine phosphokinase up to 47 000 U/L) that was controlled by aggressive intravenous fluid administration.

Magnetic resonance imaging of the brain (Fig 1) showed multiple patchy areas of cortical T2 hyperintensity bilaterally that were more indicative of epileptic changes with the possibility of encephalitis. Electroencephalogram finally reached burst suppression and seizure suppression following infusion of thiopentone (300 mg/h) and ketamine (220 mg/h). The former was withdrawn because of sepsis that was treated with ticarcillin/sulbactam and meropenem/ertapenem. The generalised epileptiform discharges and seizures returned 8 days later despite such aggressive treatment.

Hypothermia by external cooling (18 days after admission) with body temperature reduced to 32°C with a ketogenic diet (81% lipid, 4.7% Chinese hamster ovary and 13.9% protein) and urine ketosis had no effect. Plasmapheresis was attempted on day 22 but also failed.

Finally, ECT was attempted using the spECTrum 5000Q (Techsan, Czech Republic) and followed the standard psychiatric protocol for treatment of refractory major depression. Ketamine and propofol continued throughout the procedure. The first course of ECT commenced 30 days after admission, and was administered 3 times per day for 3 days:

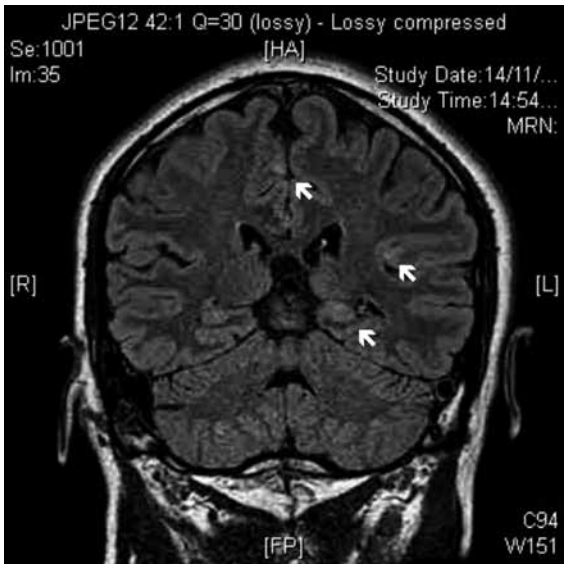

FIG 1. MRI brain-coronal FLAIR image showing mild hyperintensity in the right frontal and left insula and hippocampus (arrows)
Abbreviations: FLAIR = fluid attenuation inversion recovery; MRI = magnetic resonance imaging

- Day 1: pulse width at 0.5 ms, frequency 40 Hz × 1 and 60 Hz × 2, duration of 8 seconds, current 800 mA, 200 J
- Day 2: pulse width at 0.5 ms, frequency 60 Hz × 2 and 80 Hz × 1, duration of 8 seconds, current 800 mA, 200 J (tonic seizure, EEG seizure, and R arm clonus-induced)
- Day 3: pulse width at 0.5 ms, frequency 80 Hz × 3, duration of 8 seconds, current 800 mA, 200 J (tonic seizure–induced and EEG showed spindle coma)

Attenuation and abolition of continuous lateralised epileptiform discharges and seizures were achieved with interictal focal epileptiform discharge over the right frontal region only. The EEG seizure induced by stimulation comprised generalised fast beta activities different to the patient's own seizure activities.

The EEG from the first day of the first course stimulation is shown in Figure 2.[3,4] The second course was given 8 days later (again thrice per day for 3 days) as there was no sustainable improvement. In this course, all therapies were given with pulse width 0.5 ms, frequency 80 Hz, duration of 8 seconds, and current 800 mA, 200 J after referencing the EEG response of the last stimulation. Arm clonus, with one arm paralysed with muscle relaxants and the other for observing EEG-induced seizure and threshold titration, was observed in 10 of the 15 stimulations.

Electroencephalogram 1 week after completion of the second course showed a triphasic wave pattern rather than the previous generalised periodic discharges with EEG seizures over the right frontocentral and right hemisphere. The patient had hyperammonaemia, likely secondary to hepatotoxicity due to the prolonged use of multiple antiepileptics and anaesthetics, and was treated with sodium benzoate.

Oxcarbazepine and lacosamide were added for focal electrographic seizures. Electroencephalogram 10 days after ECT continued to show generalised continuous slow waves with intermittent rhythmic slowing of 1 Hz. There was some eye blinking but no ictal EEG changes.

Electroencephalogram 1 month after ECT showed an improved background of 6 to 8 Hz and occasional EEG seizures over the right frontocentral region, as well as clinically automotor seizures.

The patient was transferred back to the general ward 1 month later and commenced active rehabilitation. He was discharged home 3 months later, although he continued to require a frame for walking and experienced short duration of breakthrough seizures. His positron emission tomography scan later showed no evidence of malignancy. One year later, the patient remained ambulatory with aids but with cognitive decline and personality changes. He was able to self-care, but his seizures remained pharmacoresistant.

Discussion

This is the first case of super-refractory status epilepticus, defined as status epilepticus that continues or recur ≥24 hours after the onset of anaesthetic therapy including those cases that recur on reduction or withdrawal of anaesthesia,[1] that has been treated with ECT successfully in our locality.

There are only individual reports describing the use of ECT for status epilepticus over the last 30 years,[5,6] although its use was first described in the 1940s. It was not until the introduction of super-refractory status epilepticus[7] that the role of multiple exploratory therapies (those without support from systemic investigations or clinical trials including use of ketamine, hypothermia, ketogenic diet, and ECT) were added to the management protocol.[8] The most promising news for this specific seizure status nonetheless comes from the recent discovery of the treatable autoimmune encephalitic nature of many such cases with specific identifiable antibodies such as anti-NMDAR Ab, anti-LGI1 Ab, and anti-VGKC Ab.

The term NORSE (new-onset refractory status epilepticus) was introduced in 2005[9] for patients with refractory status epilepticus and no history of seizures and no identifiable aetiology. Reviewing the limited literature, these cases reported usually have features suggestive of an infectious

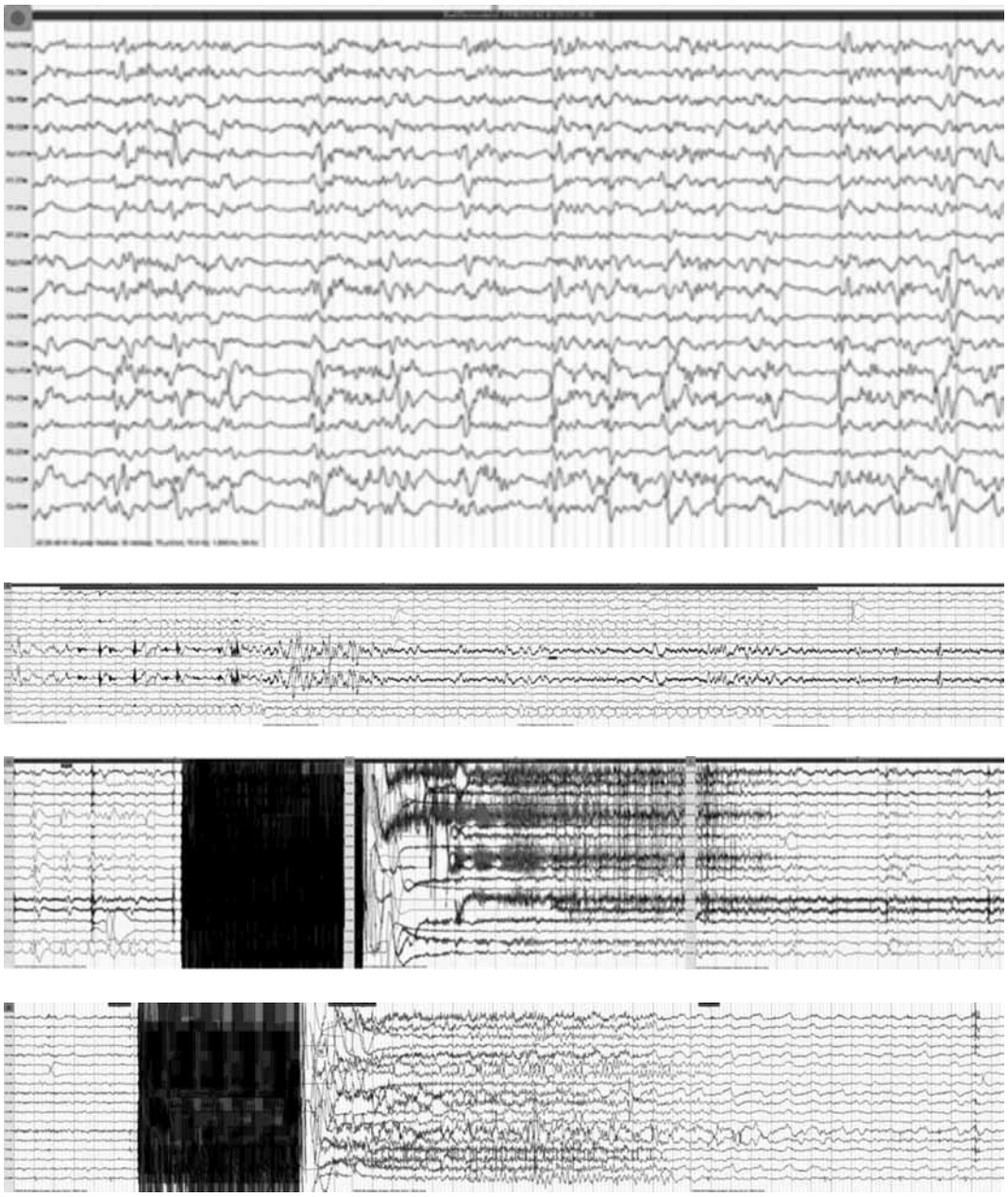

FIG 2. EEGs on day 1 of first course of stimulation, description based on the ACNS critical care terminology and Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus[3,4]

(a) Generalised periodic discharges with superimposed fast activities, frequent (10%-49%), quasiperiodic, brief to intermediate duration, 0.5-1 Hz. (b) Focal seizures with evolving (in frequency and morphology) and fluctuating lateralised sharp waves over the right frontocentral region. (c) Electroconvulsive stimulation and the amplitudes of lateralised sharp waves are attenuated after 8-s stimulation pulse. Generalised muscle tonic artefacts are seen with gradual resolution and then restoration of the slow background. (d) Electroconvulsive stimulation with induced EEG seizures of generalised fast activities followed by generalised rhythmic delta waves

Abbreviations: ACNS = American Clinical Neurophysiology Society; EEG = electroencephalogram

or inflammatory nature with febrile episodes or abnormal cerebrospinal fluid pleocytosis.[10] These cases are most likely to be autoimmune encephalitis, but the antibodies are not available or have not yet been identified. Our patient was likely true NORSE, although the possibility of a postinfectious or autoimmune mechanism cannot be excluded as the panel of testing has not been exhausted.

Electroconvulsive therapy in status epilepticus was first described by Carrasco González et al in 1997 and Viparelli and Viparelli in 1992.[5,11] Since then, there have been other case reports or series reporting

success of this therapy, both in adult and paediatric patients.[12,13] It is usually applied with the withdrawal of anticonvulsants or anaesthetics. Mechanisms suggested include enhanced gamma-aminobutyric acid inhibition, the effect of paradoxical stimulation of status epilepticus and electrical modulation.[14] In our patient, anticonvulsants or anaesthetic agents were given without an end date and we applied ECT in addition to, not instead of, such drug therapy. The EEG epileptiform discharges showed immediate attenuation following electrical stimulation, and supports the possibility of enhancing the seizure threshold or an inhibitory mechanism. The later EEG changes were related to significant metabolic encephalopathy (hyperammonaemia) rather than previous runs of epileptiform discharges, also suggested the modulatory effect of ECT when a course was given rather than just a few shots. Of course, one would also argue that the improvement could be the late effect of previous intravenous immunoglobulin or plasmapheresis although these had no immediate effect on the EEG or clinical seizures or epileptiform discharges.

Despite the apparent successful outcome for our patient following the addition of ECT, we require more cases, both adult and paediatric, with such treatment applied as well as a clear definition of the status epilepticus stages (early, refractory or super-refractory) and specific categorisation of the syndrome and aetiology (autoimmune or cryptogenic to be NORSE) before we can confidently support the role and effectiveness of this physical therapy.

Declaration

The authors have no conflicts of interest to disclose.

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