Clinical commentary

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Avoiding anaesthetics after multiple failed drug-induced comas: an unorthodox approach to management of new-onset refractory status epilepticus (NORSE)

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ABSTRACT – New-onset refractory status epilepticus (NORSE) is a rare, poorly understood and often catastrophic condition. There is little guidance available for management. Here, we describe the course of a 19-year-old man with NORSE who was treated successfully with a new approach. Our patient was initially treated with first-, second- and third-line agents including a total of seven failed drug-induced coma courses until the 30th day of hospitalization. When withdrawal of care was contemplated, management was then assumed by dedicated epileptologists and treatment course was changed. An unorthodox decision was made to avoid IV anaesthetics unless there were generalized bisynchronous tonic-clonic or generalized non-convulsive (electrographic) seizures. This approach allowed real-time assessment of treatment response to aggressive non-sedating AED therapy while the multifocal convulsive and non-convulsive seizures were ongoing. It also eliminated potentially fatal IV anaesthetic-induced complications and prevented anaesthetic withdrawal seizures. This was effective in achieving full recovery in our patient. The patient's awakening also changed the perspective of family members and care providers, avoiding premature withdrawal of care, which is often the cause of death in similar patients.

Key words: NORSE, status epilepticus, IV anaesthetics, treatment, lidocaine, coma

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NORSE is defined as "new-onset refractory status epilepticus" without a clear, acute or active structural, toxic, or metabolic cause in a patient without active epilepsy or other pre-existing relevant neurological disorder (Hirsch *et al*., 2018).

There is limited guidance in the current literature for treatment of NORSE and super-refractory

status epilepticus (SRSE) (Treiman *et al*., 1998). Conventionally, after failure of first-, second- and third-line agents, drug-induced coma is initiated with anaesthetics such as midazolam, propofol or pentobarbital with the goal of suppressing seizures or background activity for 24 - 48 hours and then to wean off sedation and reassess. Once this stage is reached, it is common practice to reintroduce sedation every time the seizures recur and continue optimizing the non-sedating AEDs (Novy *et al*., 2010; Rossetti *et al*., 2011; Ferguson *et al*., 2013, Gaspard *et al*., 2015). However, determination of the efficacy of treatment has to await the loss of anaesthetic effect, which may take a long time, particularly with pentobarbital.

Here, we describe the clinical course and treatment of a patient who was initially treated with a conventional approach without success. After seven failed attempts of both short (one-day) and prolonged (four-day) drug-induced coma courses, an epileptology team was consulted at a time when withdrawal of care was considered. A decision was then made not to reintroduce drug-induced coma unless there were clinical bisynchronous generalized tonic-clonic or generalized non-convulsive (electrographic) seizures. The reasoning for this approach was based on several observations:

– the association of IV anaesthetic use with more deaths and complications such as metabolic abnormalities (acidosis), ileus or bowel ischemia, infections (pneumonia) or deep venous thrombosis (DVT) (Ferguson *et al*., 2013; Sutter *et al*., 2014; Trinka *et al*., 2015);

– the increased risk of withdrawal seizures during the weaning of anaesthetic agents;

– and the inability to assess seizure response to AEDs in real time due to drug-induced coma.

Case study

Our patient was a previously healthy 19-year-old gentleman who presented to a community hospital for seizure-like activity. He had returned from a vacation in the Caribbean, a few weeks prior to his presentation. After his trip, he was noted to have headaches and nausea without fever. The day prior to his presentation, he had several episodes of behavioural arrest followed by weird behaviour and confusional state, suggestive of focal impaired awareness seizures. He reportedly had several generalized tonic-clonic (GTC) seizures after his presentation. Blood counts, basic chemistry, drug screen, and head CT were all normal. He was treated with lorazepam and levetiracetam prior to being transferred to our institution for a higher level of care. On arrival to our institution, the patient was lethargic and mildly encephalopathic but able to follow commands; he was initially managed by neurohospitalists and intensivists with intermittent 'curbside' epilepsy specialist assistance. Intermittent left facial twitching was noted. A contrasted brain MRI was normal and a lumbar puncture revealed clear colourless CSF with 61 white cells (75% lymphocytes), protein of 40 mg/dL, glucose of 58 mg/dL, negative OCB, and normal IgG index level. Viral meningoencephalitis was suspected due to his CSF profile and travel. He was started on acyclovir. Bacterial meningitis coverage with ceftriaxone and vancomycin was also initiated and continued until his cultures were negative. CSF bacterial cultures, Gram staining, HSV 1/2 PCR, and VZV PCR all came back negative.

Initial video-EEG monitoring showed right frontal LPDs plus superimposed spikes. Levetiracetam was increased and valproic acid was started. Overnight video-EEG captured 3-5/hour electrographic focal ictal discharges (non-convulsive seizures), maximal in the right frontal region (Fp2 >> F8 > F4), each lasting approximately 40-70 seconds. Interictally, a pattern of continuous LPDs + superimposed fast activity was noted in the same region. Over the following five days, he exhibited continuous (3-6 per hour) electrographic multifocal ictal discharges (non-convulsive seizures), about half of which were associated with clinical focal motor (convulsive) seizures mainly manifesting with left facial and left upper extremity rhythmic twitching, with spreading to bilateral facial structures and upper extremities. Electrographically, when visible in between convulsive seizures, right frontal focal electrographic ictal discharges (non-convulsive seizures) would spread to the left frontal and then to the bilateral temporal regions, attaining a widespread bi-hemispheric field (*figure 1*). On Day 3 most of the non-convulsive seizures clinically became associated with behavioural arrest and staring. Due to the widespread bihemispheric nature of seizures impairing the patient's awareness and without clear recovery in between seizures, the electroclinical diagnosis was escalated to non-convulsive status epilepticus (NCSE) with intermittent emergence of convulsive seizures. With this diagnosis, more aggressive treatments were tried. The seizures continued and on Day 6, the patient required intubation for airway protection due to worsening mental status despite efforts to avoid intubation. Anaesthesia was initiated with midazolam as it was needed for endotracheal tube irritation/tolerance and seizure management. Neither seizure suppression nor burst suppression could be achieved with midazolam infusion at 10 mg/hour. Midazolam was then switched to propofol with burst suppression requiring high doses. Seizures continued at lower doses and propofol was eventually switched to pentobarbital. For the next several weeks, multiple anti-epileptics and anaesthetics were used in attempts to wean from barbiturate

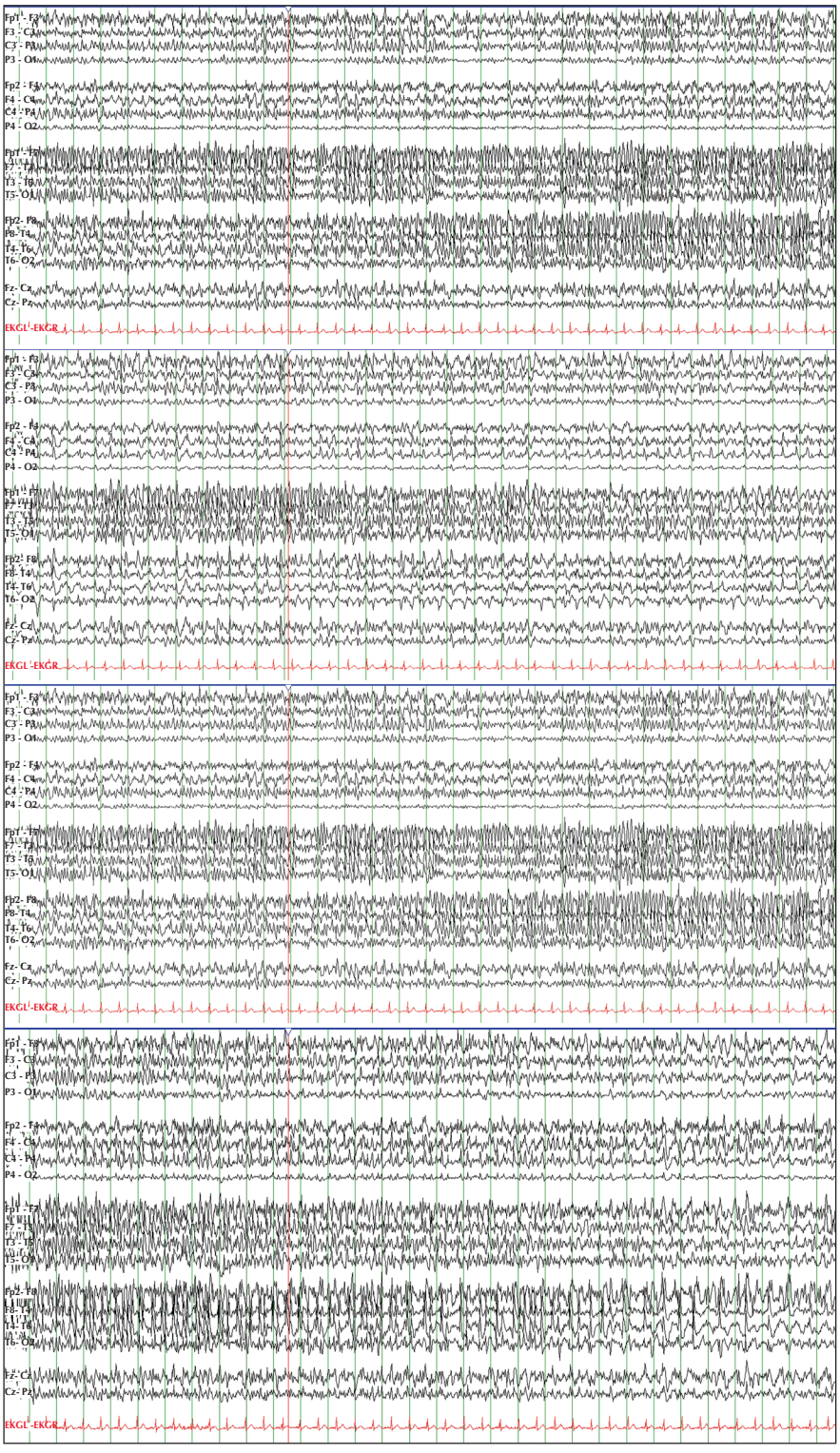

Figure 1. EEG showing right frontal focal electrographic ictal discharges (non-convulsive seizures) spreading to the left frontal and then to the bilateral temporal regions, attaining a widespread bi-hemispheric field.

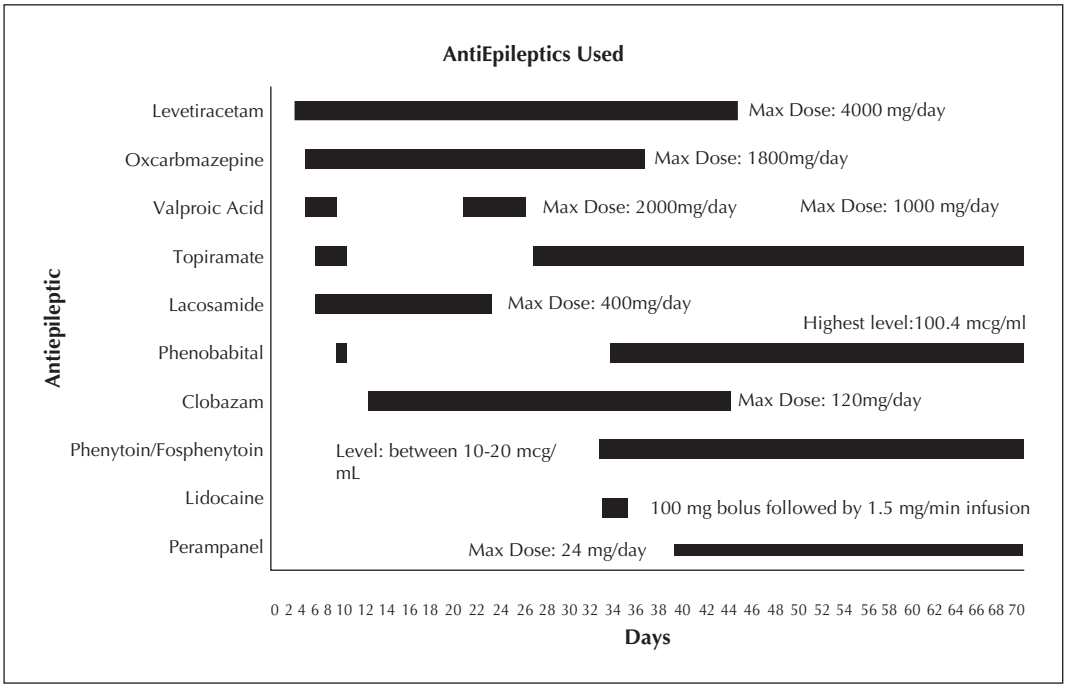

Figure 2. Antiepileptics used during our patient's hospitalization. Maximum dosages are listed.

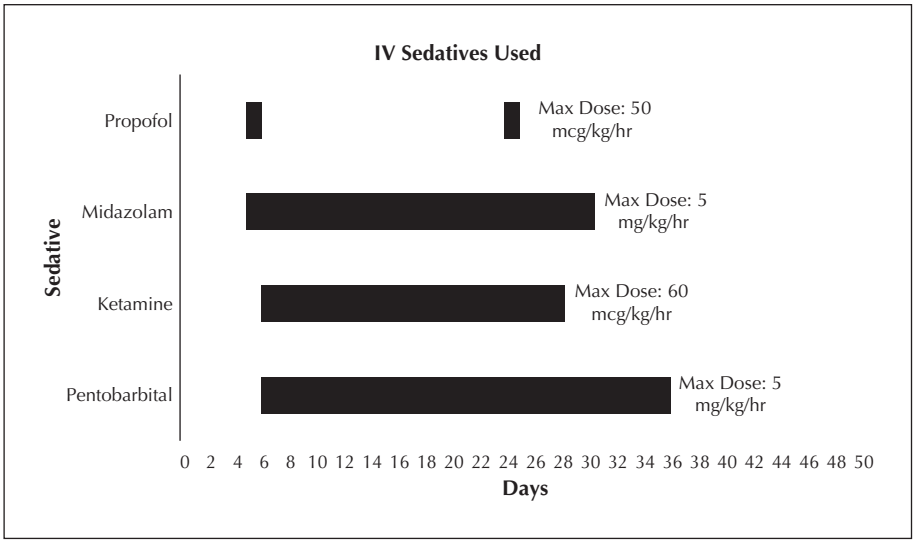

Figure 3. Anaesthetics and sedatives used. Dosing was done to achieve burst suppression. Pentobarbital was transitioned to phenobarbital at Day 34.

coma. AED and anaesthetic administration courses are outlined in *figure 2, 3*.

An extensive workup looking for infectious, autoimmune, inflammatory or structural causes of his seizures was undertaken and only notables for a high titre of anti-GAD-65 antibodies (>1: 4,800; positive considered to be >1:1200). A tentative diagnosis of NORSE secondary to anti-GAD 65 antibodies was made as per several reports describing a role of GAD antibodies in NORSE and autoimmune epilepsy (McKnight et al., 2005; Errichiello *et al*., 2009; Liimatainen *et al*., 2010; Dubey *et al*., 2017; McKeon and Tracy, 2017). He was treated with five days of plasma exchange, high-dose steroids, and eventually IVIG (0.4 g/kg/day for five days). The ketogenic diet was initiated and maintained throughout hospitalization, only intermittently achieving ketone levels at 80 mg/dL. There was no immediate or delayed response to these treatments within the

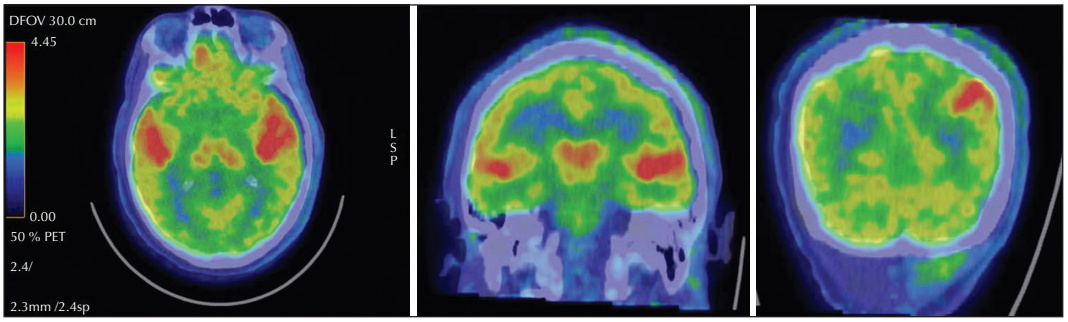

Figure 4. Brain PET revealing heavy uptake in bitemporal, right frontal, and left parietal regions, suggestive of ongoing multifocal seizures.

first 30 days of admission. Rituximab was initiated with a first dose on Day 22. Brain PET revealed heavy uptake in bitemporal, right frontal, and left parietal regions, suggestive of ongoing multifocal seizures (*figure 4*).

Convulsive and non-convulsive seizure activity consistently resumed at higher frequencies of 10-20 per hour with every pentobarbital wean (*figure 5*). On Day 30, given the potential high mortality and in the case of survival, a devastating outcome with major deficits potentially requiring nursing home placement was discussed between the family, neurohospitalists, and intensivists but not the peripherally-involved epileptologists. Withdrawal of care was considered. At this point, epilepsy service assumed the care of the patient. Continuation of aggressive support/treatment was recommended by the epileptologist for several reasons:

– the seizures were multifocal in nature even though often widespread and bihemispheric both on EEG and clinically;

– brain MRI on Days 1, 6 and 19 were normal suggesting no immediate brain injury;

– and the patient was a 19-year-old with no medical comorbidities or complications during his course.

The presumed autoimmune nature of the patient's condition also favoured a good outcome (Holzer *et al*., 2012). Considering the above factors and the earlier listed risks associated with IV anaesthetic use, a decision was made not to reintroduce drug-induced coma unless there were clinical bisynchronous generalized tonic-clonic or generalized non-convulsive seizures.

Between Days 30 and 37, another wave of aggressive non-sedating AED escalation took place with discontinuation of ineffective AEDs and introduction of new ones *(figure 2)*. Perampanel (PER) was introduced and titrated up to 12 mg TID. About 12 hours after the addition of PER on Day 36, the patient's clinical multifocal motor seizures stopped and never recurred, however, non-convulsive seizures continued at a rate of 10-20 per hour. Phenobarbital blood levels were initially around 60 mcg/mL; then, the blood levels were pushed as high as 90-100 mcg/mL. A high blood level of phenobarbital was aimed for as per several reports of successfully treated refractory status epilepticus (RSE) cases with very-high-dose phenobarbital, with blood levels reaching up to 250 mcg/mL (Crawford *et al*., 1988; Lee *et al*., 2006; Watanabe *et al*., 2014; Uchida *et al*., 2016).

On Day 37, due to the absence of IV anaesthetics, the patient's interictal EEG became more organized with a continuous delta and superimposed alpha/beta background. Clinically, the patient started to have intermittent spontaneous blinking and at times spontaneously opened his eyes, but non-convulsive seizures continued at the same frequency. On Day 42, lidocaine was initiated with a loading dose of 100 mg, followed by 1.5 mg/min IV infusion for 24 hours. This agent was used per reports of RSE termination with lidocaine (Zeiler *et al*., 2015). Ten hours and 37 minutes after the initiation of lidocaine (Day 43), non-convulsive seizures stopped abruptly and never returned. Notably, seizures continued at the same frequency after the loading dose and initial 10.5 hours of lidocaine infusion until stopping abruptly. Delayed response to lidocaine infusion has been previously reported (Rey *et al*., 1990). On Day 50, the patient received his second dose of rituximab and no other doses were given.

Two to three days after cessation of all seizures, we started a gradual taper of phenobarbital and other AEDs. Over the following days and weeks, the patient was able to speak, eat independently, and walk on his own. He was discharged to inpatient rehab on hospital Day 70. He presented in the clinic, 92 days after his initial presentation, with no neurological deficits beyond subtle ataxia and slower speech patterns which resolved after phenytoin was tapered off. A two-hour video-EEG returned normal and plans were made to taper topiramate as well. His other AEDs included PER at 12 mg qhs and phenobarbital at 30 mg qid.

Discussion

The current case illustrates a new approach with successful management of NORSE in a patient who was

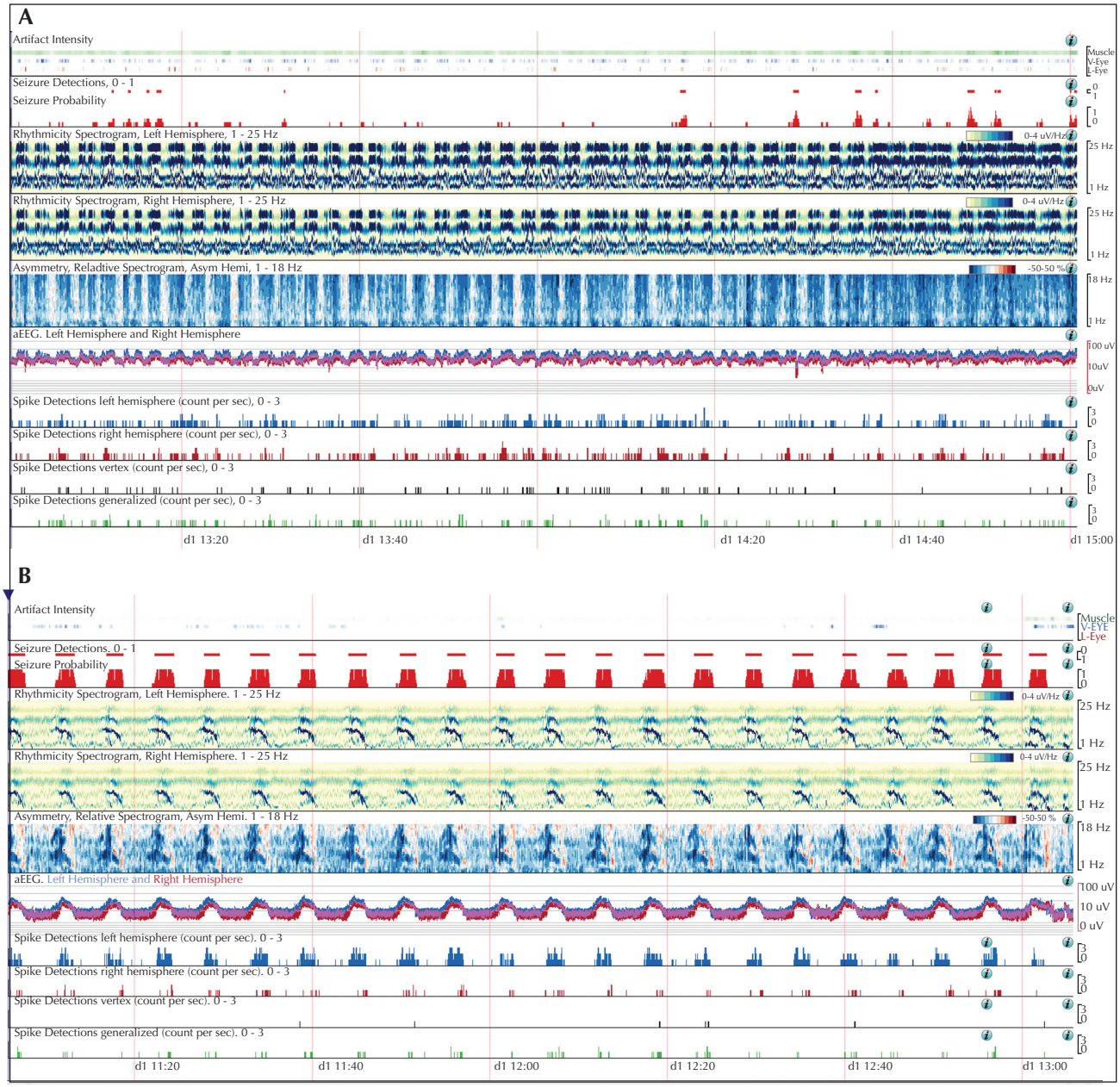

Figure 5. EEG showing consistent resumption of convulsive (A) and non-convulsive (B) seizure activity at higher frequencies of 10-20 per hour upon weaning off pentobarbital.

initially treated with a conventional approach which led to over-treatment with anaesthetics, failure of seizure control, and consideration of withdrawal of care.

Dedicated management by an epileptologist is often unavailable and intermittent although this may be different between academic institutions and tertiary hospitals. It is considered common practice that these patients get managed by general neurologists or intensivists with 'curbside' assistance by an epileptologist when available. This could be addressed further by future studies for improvement in the earlier management of RSE. There are no clear treatment guidelines for RSE or SRSE. As a result, treating physicians generally extend typical convulsive status epilepticus guidelines to these patients, which is often appropriate but can lead to over-treatment. Once third-line treatment with IV anaesthetics is initiated and failed, as it was in this patient, it is quite difficult and unorthodox to change the course and try to avoid IV anaesthetics, as this would mean the patient would be allowed to have seizures. Over

the years, there has been an increasing number of reports showing more favourable outcomes in patients who were awake or had focal SE at presentation (Leitinger *et al*., 2019). There has also been an increase in the number of reports showing radiological markers for neuronal injury during status epilepticus (Parmar *et al*., 2006; Cartagena *et al*., 2014; Mendes and Sampaio, 2016). Based on these facts, we hypothesized that generalized bisynchronous seizures would be more injurious to the brain than the focal ones. As our patient had multifocal seizures and consistently demonstrated no abnormalities on brain MRI scans, we decided not to resume IV anaesthesia unless there were generalized bilateral tonic-clonic or generalized electrographically bihemispheric/bisynchronous non-convulsive seizures. Our decision was also influenced by the reports showing higher mortality rates in patients with SE who were treated with aesthetic agents (Litt *et al*., 1998; Koubeissi and Alshekhlee, 2007). One study showed a nearly three-fold mortality rate independent of possible confounders for the patients who received IV anaesthesia for status epilepticus (Sutter *et al*., 2014). This approach allowed more effective real-time assessment of response to non-sedating AEDs and other treatment modalities, while eliminating the serious potential complications of IV anaesthetics. An additional potential benefit of this approach is keeping the patient awake and responsive during the treatment process which changes the perspective of both the family and treating physicians, decreasing the chances of premature withdrawal of care, which is common in these circumstances. To our knowledge, this approach for selected patients has not been reported before.

The current mortality rate associated with NORSE and SRSE is high but variable between 23-60% and affected by the underlying aetiology and type of status (Gaspard *et al*., 2015; Hirsch *et al*., 2018; Kellinghaus *et al*., 2018). Autoimmune aetiologies tend to have lower mortality rates compared to structural aetiologies (Holzer *et al*., 2012; Alvarez and Drislane, 2016; Chen *et al*., 2018). We hypothesize that not only the malignant nature of these conditions, but also the prolonged drug-induced coma(s) with direct and indirect potential harm to the patients, contribute to this high mortality rate (Koubeissi and Alshekhlee, 2007; Ferguson *et al*., 2013; Sutter *et al*., 2014; Trinka *et al*., 2015). By "indirect", we mean the potential issues that can arise in the absence of dedicated epileptologist support. Often non-epileptologist-treating teams have the urge to suppress seizures regardless of the nature or classification of seizures. Any clinical seizure, even focal motor seizures, can be very disturbing for families and care providers; resulting in reflex resumption of anaesthetic agents. This can lead to over-treatment and prolonged recurrent drug-induced coma(s) for as long as many months, astronomically high hospital costs, and eventual consideration of poor prognosis and grave nature of the condition resulting in premature withdrawal of care. Our patient was very close to this outcome. We do think our patient was treated appropriately with the conventional method initially. The decision to use anaesthetics was also appropriate considering the diagnosis of status epilepticus (both convulsive and non-convulsive) without recovery in between seizures and worsening mental status of the patient. However, the question of when to avoid anaesthetics begs the answer. Would it be appropriate to change the course after five or more failed drug-induced coma attempts in selected patients? This could be best answered by future controlled trials. Our patient did very well but we cannot overemphasize the fact that our patient's seizures were classified as focal by the epileptologist, even though there was often bilateral facial and bilateral upper extremity involvement clinically and bihemispheric involvement electrographically. Our decision to avoid anaesthetic agents resulted in a lot of unrest among the non-epilepsy care providers including doctors, nurses and family members, initially due to ongoing seizures which is another reason why these patients get over-treated. When the patient started to wake up with spontaneous blinking and tracking with his eyes, initially his family members' perspective changed and when his clinical convulsive seizures stopped, non-epilepsy care providers's perspectives changed. After all seizures stopped, we were able to gradually lower the doses of non-sedating AEDs which resulted in quicker than expected recovery since there were no IV anaesthetics on board.

It is quite difficult to determine what ultimately achieved full seizure control in this patient. There was a temporal relationship between the use of PER and lidocaine and cessation of convulsive and non-convulsive seizures, respectively. Though there is only limited evidence supporting PER use in RSE or SRSE, the number of case reports and case series supporting its efficacy has increased over the past several years. A success rate of about 16.2-30% was reported in some studies (Redecker *et al*., 2015; Strzelczyk *et al*., 2019). However, PER was often the fourth, fifth or sixth drug used. One recent and relatively larger review reported 40.1% success for the treatment of RSE (Ho *et al*., 2019). In this study, responders were defined as patients who received PER as the last AED, stopped having seizures within the four days of treatment initiation, and stayed seizure-free thereafter. It appeared that focal motor or convulsive status epilepticus patients had better response to PER, however, that was attributed to selection bias. PER use in RSE and SRSE also makes sense at cellular and molecular level as it is a selective non-competitive antagonist of AMPA receptors, the major subtype of ionotropic glutamate receptors. Animal

studies have shown a progressive decrease in synaptic GABA receptors and increase in synaptic NMDA receptors potentiating excitation (Mazarati and Wasterlain, 1999; Chen and Wasterlain, 2006; Naylor *et al*., 2013). In our case, considering the multiple agents used for the treatment, it is not clear if we can attribute the seizure suppression solely to PER and lidocaine. It cannot be determined whether the cause of seizure cessation was due to the disease running its course, that the immunotherapy started to work, that the right AED combination and levels were achieved, or some combination of these. What can be stated with certainty is that our approach with avoidance of general anaesthesia allowed us to more accurately observe the onset of improvement in real time, avoid premature withdrawal of care, and ultimately better manage our patient.

Conclusion

This case report describes a different treatment approach that requires further investigation. Larger randomized and controlled studies are needed to determine whether it would be appropriate to avoid IV anaesthetic agents in selected (focal status epilepticus) patients after five or more failed drug-induced coma courses. This approach may have several benefits including better non-sedating AED optimization with real-time assessment of seizure response. It can also prevent potential fatal complications related to IV anaesthetic agents, decrease the cost of care, and keep the patient awake during treatment, helping to prevent premature withdrawal of care, which is more likely in a comatose patient. □

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

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

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TEST YOURSELF

(1) What is new-onset refractory status epilepticus?

(2) What are the common complications associated with prolonged use of IV anaesthetics?

(3) What is the mechanism of action of perampanel and how could that apply to the treatment of refractory status epilepticus?

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".