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How I Treat Status Epilepticus in the Neuro-ICU

Panayiotis N. Varelas

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Abstract Status epilepticus still remains a formidable adversary to neurointensivists. Although the majority of cases admitted to the Neuro-ICU are easily controlled with one or two antiepileptic drug defense lines, several cases become refractory and end up receiving general anesthetics for days or weeks with significant morbidity. Treatment algorithms have been published and should be followed, but in many cases they are inadequate because, especially in the distal branches of the treatment tree, are based on anecdotal data or small series of patients. In addition, a double-blind, randomized-controlled study in status has not been done for many years and solid data are lacking for the newer antiepileptics. Therefore, in the moderately to severely refractory cases, status treatment is based on personal previous experience and becomes an art more than a science. In this review of a difficult case, we discuss some fine details of the treatment provided and emphasize the multidisciplinary approach that should be followed including involvement of neurointensivists, epileptologists, electroencephalographers, and neurosurgeons.

Keywords Status epilepticus · Treatment · Neuro-ICU

Case Report

A 54-year-old African American man was transferred to our hospital for management of his seizures. He had a history of neurosarcoidosis, diagnosed several years prior via brain biopsy (was on prednisone and previously on azathioprime and cyclophosphamide), epilepsy (on phenytoin, levetiracetam, gabapentin, and oxcarbazepine), and panhypopiyuitarism (on levothyroxin, androgens and desmopressin). These seizures were generalized tonic–clonic convulsions with left gaze deviation. On admission to the Epilepsy monitoring unit (EMU) he was found to be in complex partial status epilepticus, with recurrent seizures every 5–10 min emanating from the right centrotemporal regions (Fig. 1). Brain MRI showed several scattered enhancing lesions in both hemispheres (Fig. 2). Despite 10 mg dexamethasone IV, several doses of lorazepam IV and optimization of his phenytoin levels, he continued seizing and the next day he was transferred to the Neurosciences Intensive Care Unit (NICU), where he was intubated, given 200 mg Phenobarbital IV, connected to a continuous electroencephalogram (CEEG) monitoring and eventually placed on pentobarbital coma (10 mg/kg IV load and 2.5 mg/kg/h continuous infusion) after a small bolus of midazolam (5 mg IV) failed to stop the seizures. Oxcarbazepine was discontinued, dexamethasone was continued at 4 mg q6 h IV and the barbiturate infusion was titrated to achieve burst-suppression EEG pattern with suppression of 20–30 s. Because of hypotension, he initially required 3 l normal saline boluses IV and neosynephrine infusion. He remained on deep barbiturate coma for 2 days and subsequently he was weaned off the next day (post-admission day [PAD] 4). The following day's CEEG showed quasi-periodic right centroparietal sharp wave discharges, but on PAD 5 he had 17 subclinical seizures and on PAD 6 eleven. Slowly he emerged from coma, but had left hemiplegia and only rarely he did respond to verbal commands. He also developed a pneumonia, which was treated with antibiotics and eventually was extubated on PAD 8. Because of continuing complex partial seizures, intracranial electrodes were placed on

P. N. Varelas (✉)
Department of Neurology, Henry Ford Hospital, K-11, 2799 West Grand Blvd, Detroit, MI 48202, USA
e-mail: Varelas@neuro.hfh.edu

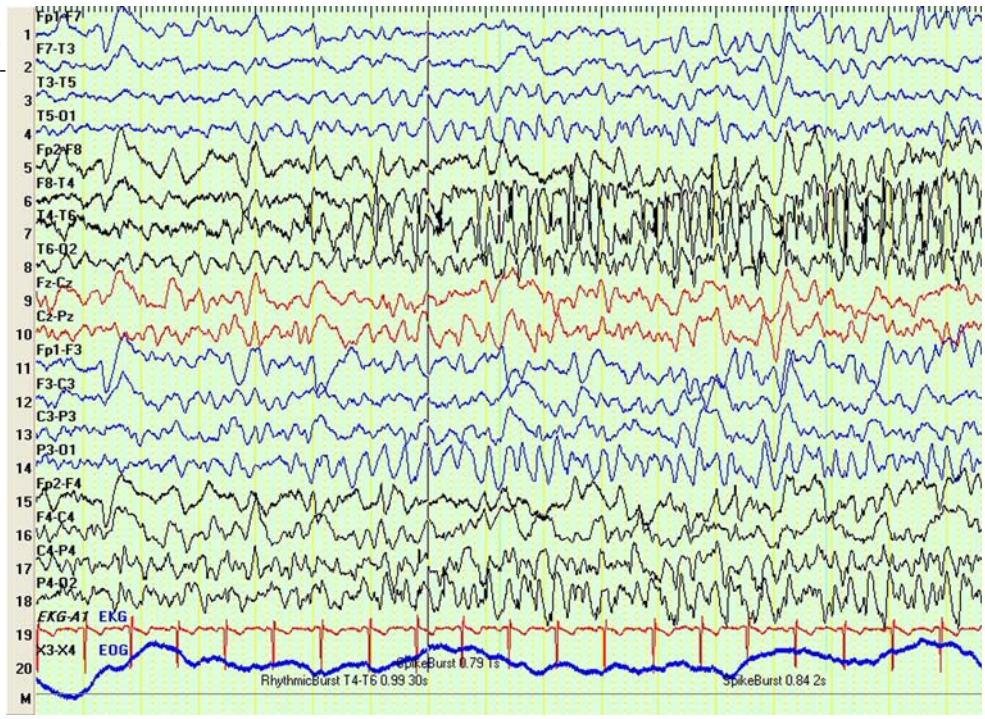

Fig. 1 Continuous electroencephalogram (20 s époque) showing the onset of a seizure (mid-right side of the recording) emanating from the right parietal-temporal areas

PAD 14 and the patient was again monitored in the EMU. Over the next 5 days 71 subclinical seizures were recorded. The right parietal epileptic focus was resected on PAD 20 and the postoperative EEGs showed only interictal discharges in the right frontal areas and mild background slowing. His mental status improved significantly to the point that he was discharged to rehabilitation on PAD 30 on p.o. levetiracetam 1,000 mg q8 h, phenytoin 100 mg q8 h, phenobarbital 30 mg at night and valproic acid 750 mg q8 h.

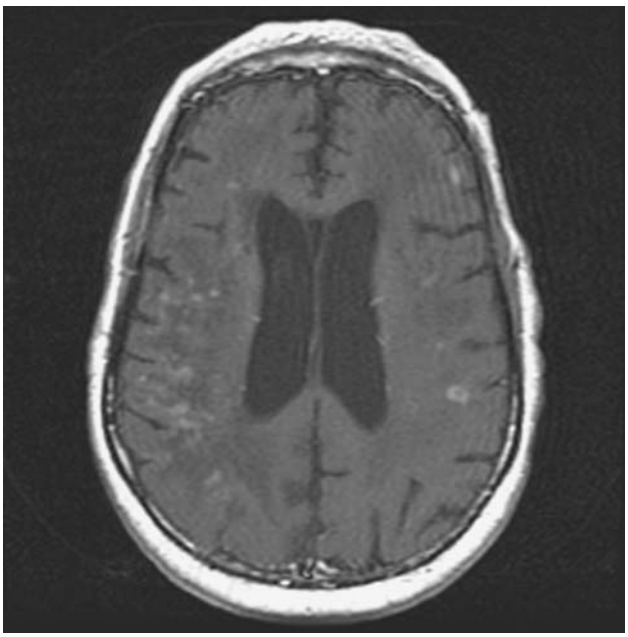

Fig. 2 T1 MRI of the brain after Gadolinium enhancement showing multiple small enhancing lesions within the perivascular spaces in both hemispheres

Comments

Refractory status epilepticus (RSE) is defined as status not controlled after the initial parenteral therapy with a minimum number of standard "front-line" antiepileptic drugs (either two or three) or status with a minimum duration of seizures that persist despite treatment (either for 1 or 2 h) [1, 2]. When these measures fail, patients are usually intubated, placed on mechanical ventilation and sedated with general anesthetics.

I follow this approach when I treat RSE. My aim is to treat the patient as a neurological emergency (the sooner the seizures are treated, the sooner the status is controlled [3] and the better the outcome [4]). After the patient receives lorazepam (up to 0.1 mg/kg IV) and is loaded with phenytoin (20 mg/kg IV or fosphenytoin equivalents or IV valproic acid—*vide infra*—in case of phenytoin allergy), if he is still seizing, he is transferred to the NICU, where he is connected to CEEG monitoring and is intubated and mechanically ventilated (with a goal to avoid hyperventilation, which may exacerbate seizures [5], i.e., to a $PaCO_2$ level of 40–45). If RSE is de novo or there is suspicion of a new intracerebral insult, a computerized tomography or magnetic resonance imaging study of the head is performed

(while the CEEG leads are off to avoid artifacts) in order to assess the presence of treatable causative lesions, such as intraaxial or extraaxial masses. Special attention is paid into checking glucose, antiepileptic drug trough, sodium, ionized calcium and magnesium levels (low levels of which could represent easily treatable causes of seizures and should not be missed) and administering thiamine IV. I also add, vitamin B6 (either as IV pyridoxine hydrochloride or as enteral B6 at a dose of 100–300 mg/day), a cofactor in the synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid [6]. It is cheap and non-harmful, but there are not many data about its usefulness, except in children with pyridoxine-dependent seizures or in adults with isoniazide intoxication or during pregnancy [7]. If the patient is hypertensive or has supraventricular arrhythmias, I prefer to specifically use calcium channel blockers, such as verapamil (IV initial dose 0.075–0.15 mg/kg over 2–3 min, followed by infusion 0.125 mg/min or enterally 120–240 mg/day), a drug with either direct anticonvulsant properties or action through inhibition of *P*-glycoprotein in the epileptic focus endothelium (this protein may inhibit the penetration of anticonvulsant drugs to the seizure site) [8].

The first additional anticonvulsant drug that I use in the NICU is midazolam [9]. This highly lipophilic drug can be even administered intramuscularly in case of poor venous access (at a dose of 0.2 mg/kg) without significant local irritation (as with lorazepam) and has been shown to be superior to diazepam in rapidly controlling seizures [10]. As a continuous infusion (0.08–0.4 mg/kg/h after a 0.1–0.3 mg/kg IV bolus over 2–5 min), midazolam provides the benefit of rapidly controlling seizures and allowing a rapid emergence from sedation when discontinued. During night time admissions, when less expertise may be available at the hospital, I ask my residents to start the patient on midazolam infusion. My experience with this approach is a significant reduction or complete cessation of clinical or electrographic seizures until I gain direct access to the patient's data. I also prefer midazolam to propofol, because this drug (although able to induce deeper sedation and faster emergence) can also lead to seizure-like phenomena difficult to differentiate from real seizures [11], more hemodynamic instability and the rare, but lethal, propofol infusion syndrome at higher doses [12].

Except for a small IV bolus of midazolam, this treatment option was not pursued in our patient, because, based on the response, we thought it would be insufficient to control this RSE. Instead, we used a small dose of phenobarbital as a third line antiepileptic drug, because the patient had been on this drug before as an outpatient. It also failed to control the RSE. It is noteworthy that in two surveys, both in Europe and the United States, the majority of neurologists also used this drug after failure of benzodiazepines and phenytoin to control status epilepticus [13, 14]. On the basis of the current and previous experience I had with phenobarbital, I believe that the recommended IV loading dose of 20 mg/kg (at a rate of 30–50 mg/min) [2, 15] does not confer any advantage compared to shorter acting third-line agents, such as midazolam or, eventually, pentobarbital, because in every situation the patient will need airway protection and ventilatory support anyway. I would recommend phenobarbital use only if RSE is clearly related to barbiturate withdrawal.

But even in the majority of cases that I use midazolam IV, I use it as a temporary measure in order to buy time to administer additional longer acting AEDs, such as IV valproic acid (loading dose of 15–30 mg/kg, followed by IV 6–8 mg/kg q8 h), followed, if needed, by IV levetiracetam (500–1,000 mg q12 h, up to 3 g/day, especially in patients with hepatic dysfunction) or, in the end, by topiramate (enterally at a dose of 100–400 mg/day, occasionally reaching 800–1,000 mg/day doses). These intravenously (levetiracetam and valproic acid) and enterally available medications (topiramate) have been used in SE with variable results [16–18], but none has been approved for this specific use. I follow this sequence because there are more data for valproic acid use than for the other two antiepileptics and because the availability of IV levetiracetam may convey a theoretical advantage compared to the potentially erratic absorption of any enterally administered topiramate in critically ill patients.

As I wean midazolam after 8–12 h of seizure control, by decreasing the dose by 2–4 mg q2 h, seizures may recur. In this case, I prefer to induce barbiturate coma with pentobarbital. This is an intermediate duration barbiturate (half-life approximately 24 h) offering the advantage of faster emergence compared to phenobarbital. In a metanalysis, it also appears to be superior to midazolam or propofol in controlling RSE (but with more side effects, such as hypotension) [19]. I administer it as a 6–15 mg/kg loading dose IV, followed by a continuous infusion of 0.25–4 mg/kg/h. Extra loading doses can be administered to reach a CEEG burst suppression pattern of 20–30 s. I prefer this or deeper level of sedation ("flat record") because patients with deeper suppression appear to have fewer relapses and probably better outcome [20]. I continue the barbiturate coma for 24–48 h and then allow the patient to slowly emerge by decreasing the pentobarbital infusion by 0.5 mg/kg/h q4–6 h. There are reports supporting longer (>96 h) suppression [21], but any benefits from deeper and longer suppression should be balanced against the significant adverse effects from barbiturates. These include hypotension (must keep the central venous pressure 6–8 mmHg with high infusion rates or boluses of intravenous fluids and occasionally administer pressors), respiratory depression (full ventilatory support, every 1 h endotracheal

suctioning, hourly chest percussions), ileus (necessitating total parenteral nutrition), immunosuppression and fever suppression (which may lead to "occult" sepsis), immobility (high risk for deep venous thrombosis, necessitating 5,000 units of subcutaneous heparin q8 h) and loss of the neurological examination (with occasional need to differentiate from brain death) [22].

If during emergence from pentobarbital coma status epilepticus recurs, I prefer to induce another longer (up to a week at a time) pentobarbital coma course. Nobody knows how long this process should be continued, but occasionally perseverance is rewarded. The longest successful coma in my personal experience was 6 weeks in a patient with encephalitis, but longer periods have also been reported. In case of such an agonizing refractoriness, alternative treatments such as inhalational anesthetics (isoflurane, desflurane) or ketamine should be considered [1, 2]. If during emergence from a long pentobarbital coma, seizures (but not status!) re-appear, sometimes I use a small dose of phenobarbital (30–120 mg/day p.o. and tapering over 1–2 weeks) as a "bridging" process for potential barbiturate withdrawal.

In case of a demonstrable focal lesion, as in our patient, surgical resection should be kept in mind. Instead of reinstituting a longer barbiturate coma after the first attempt failed to control the RSE in a patient, like ours, already on high-dose steroids, we decided to avoid this avenue, especially since he had a resectable epileptic focus in a non-eloquent area of the brain. Although the majority of reports are small case series [23–25], some experts advocate this treatment for any patient with medically intractable status (i.e., who fails to respond to 3 courses of cerebral suppressant therapy for approximately 2 weeks [24]) and focal EEG changes or a focal lesion on neuroimaging.

Author Biography

Dr. Varelas was born in Athens, Greece. He received his MD from the University of Athens in 1983 and subsequently completed residency in Neurology at the Eginition University Hospital in Athens Greece. After the residency he completed his PhD in neurotoxicology and worked for a brief period at Dr Stanley Appel's lab in Houston, TX. He completed a second Neurology residency, this time in the US, at Yale University School of Medicine in New Haven, CT and subsequently a Neuro-ICU fellowship at the Johns Hopkins Hospital in Baltimore, MD. Between 2000 and 2005 he served as the Director of the Neuro-ICU at the Medical College of Wisconsin in Milwaukee, WI and subsequently moved to Detroit, MI, where he is currently the Director of the Neuro-ICU at Henry Ford Hospital and an Associate Professor of Neurology at Wayne State University. He is the author of multiple papers and chapters and has served as the Editor of the only book regarding seizures in the ICU. He is also a reviewer for multiple journals and participates in several active research projects.

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