Update on Refractory Status Epilepticus

The first priority for the consulting neurologist is confirming the diagnosis. Treating any underlying disease does far more to improve outcome than mere suppression of seizures. Treatment options exist for prolonged SE, but clinicians must be realistic with families.

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A 32-year-old right handed male is brought comatose to his local emergency room after two witnessed generalized seizures at home. He receives intravenous benzodiazepines en route in the ambulance and an infusion of fosphenytoin on arrival, following two further seizures in the ER. Emergency cranial CT is normal. He is intubated and taken to the intensive care unit, where there is concern for continuing seizures. The neurology service is consulted for further management.

The formal definition of status epilepticus (SE) has changed in recent years, though the basic idea is unchanged: unremitting seizures without intervening recovery of consciousness, or a prolonged single continuing seizure. Presently, the accepted duration of ‘prolonged’ is five minutes. Thus, our patient was in SE when brought to the ER. Clinical trials in the 1980s and 1990s and the recently published RAMPART trial provide Class I evidence for the first-line treatment of SE: parenteral benzodiazepines (intravenous lorazepam or intramuscular midazolam) followed by intravenous fosphenytoin. SE at this stage can be successfully treated with just these measures; if seizures continue beyond this stage, the patient is said to have entered ‘established’ SE, which is when ER or ICU staff will usually call for a neurologist.

The first priority for the consulting neurologist—as always—is confirming the diagnosis. An actively convulsing patient should leave little room for doubt, but it is worthwhile deliberately considering and excluding non-epileptic attacks. To a practiced eye, non-epileptic seizures are easily recognized—asynchronous movements, fluctuating pattern and distractibility and specific movements such as side-to-side head motion and pelvic thrusting—but many general physicians will not have the necessary experience to make the distinction. If the patient appears still, it is worth closely examining the eyes, corner of the mouth and the thumb for a full minute. Subtle motor status can often be picked up by conjugate deviation of the eyes or nystagmoid jerking, or twitching of the mouth or thumb. Finally, continuous bedside electroencephalography (EEG) is invaluable in the management of SE: examination of the first few minutes of the trace will exclude ongoing non-convulsive status epilepticus, and may point to a spike focus or localizing abnormality. If the patient is indeed in non-convulsive SE, the only immediate priority is to abolish seizures as rapidly as possible. Options at this stage include more intravenous benzodiazepines or intravenous phenobarbital, valproic acid or levetiracetam.

A neurological examination to the extent possible should not be omitted, and should document the level of consciousness, the presence or absence of neck stiffness, fundoscopy, obvious motor asymmetry in the limbs, deep tendon reflexes and plantar responses.

There is no clinical evidence of ongoing seizures; stat EEG shows continuous slowing. On exam, the patient is GCS 8/15. There is no neck stiffness, fundoscopy is normal, and there are no focal neurological findings. The patient was previously well, apart from a minor flu-like illness a week ago, and does not have a history of epilepsy. Routine labs are normal apart from a slightly high total white count. CSF examination shows normal protein and glucose and a minor pleocytosis. The prognosis of SE overwhelmingly depends on its cause. Following emergency control of seizures, the treating team should work rapidly and efficiently to attempt to identify an
etiology. The history is crucial here: in a patient known to have epilepsy and on anticonvulsants (not the case here), the most likely cause will be missed medications, and seizures often only respond to reinstitution of the specific medication the patient takes. Related, a drug history in general (including drugs of abuse) and a urinary drug screen will exclude a toxic cause. Intracranial infection is an important, and potentially curable, cause of de novo SE: routine labs, including blood cultures if the patient is febrile, and CSF examination are all mandatory, and all patients need coverage with broad-spectrum intravenous antibiotics and acyclovir until infection screen results are confirmed negative. SE itself may cause a minor increase in CSF lymphocytic cellularity (as in our patient) and can be ignored if the rest of the tests exclude infection.

Four hours after admission to ICU the patient has further seizures characterized by whole-body stiffening and clonic jerking accompanied by a generalized ictal EEG rhythm. He has already received 8mg of lorazepam, and phenytoin levels following his intravenous load are high therapeutic. The patient is in established status, and should be put in a sedative coma for 24-48 hours, with dosing adjusted to produce a burst-suppression pattern on EEG. The agents commonly used are pentobarbital (thiopental), propofol or midazolam. ICU staff will usually have a preference for one of these agents, all of which have individual pros and cons; pentobarbital, though, continues to be the most commonly used agent. With the patient in coma, maintenance anticonvulsants should be increased to include another agent. Having the patient in coma affords the opportunity for further imaging, which should be with MRI, at high field strength (3T)—if available—with and without contrast. MRI, in general, is the imaging of choice for epilepsy, and may reveal the cause (focal lesions of various types) and/or in the acute setting, the effect of repetitive seizures (FLAIR signal change in the hippocampi, anywhere else in the gray matter, or a discrete lesion in the splenium of the corpus callosum).

There is subtle indication of bilateral hippocampal high T2 signal change on brain MRI that enhances faintly with contrast. An attempt at withdrawal of pentobarbital sedation after two days is unsuccessful, despite the patient being on sufficient phenytoin in addition to high-dose levetiracetam. The patient is re-sedated, and maintenance anticonvulsants increased to include valproic acid.

The patient has moved from established to refractory SE, defined as seizure recurrence after >24 hours of sedation. The MRI changes seen are typical for the effect of repetitive generalized, or bilaterally independent seizures, reflecting the selective vulnerability of the hippocampus. The appearances argue against infection (e.g. herpes encephalitis, which is usually asymmetric, and involves extra-hippocampal structures); the mild contrast enhancement reflects seizure-related blood brain barrier breakdown. The lack of any other lesion excludes an obvious major structural substrate for the seizures, though more subtle lesions (e.g. cortical dysplasia) remain entirely possible. The absence of gross structural pathology and normality of investigations are negative prognostic indicators at this stage because specific treatments cannot be applied. Management becomes necessarily symptomatic: escalation of maintenance anticonvulsants to high therapeutic concentrations and sedation. This situation—de novo refractory status epilepticus of unknown cause—is rare, but not uncommonly seen in referral centers. A common acronym applied is NORSE (New Onset Refractory Status Epilepticus); there may be an overlap between NORSE and other entities such as FIRES (Febrile Infection – or Fever Related—Refractory Epileptic Encephalopathy).

Three days later a further attempt at pentobarbital withdrawal is unsuccessful. The medical student on the service asks why seizures become refractory. The ICU staff and the family ask whether any other treatment modalities can be tried.

The received wisdom regarding the treatment of refractory SE is simply sedation and periodic lightening (every two to three days) under anticonvulsant cover; there is no systematic evidence for or against this approach. The hope, though, is to ‘break’ the cycle of seizures with sedation, so that on lightening the maintenance anticonvulsants are sufficient to keep seizures under control. The approach however has a certain logic, and is related to the student’s question. The chemical environment of the brain changes in response to seizures, but in a perverse fashion that fosters more seizures. Specifically, GABA receptors—the main inhibitory chemical messengers—are progressively lost from the external cell surface and migrate intracellularly; 8 the brain becomes more excitable with every seizure. Thus, the intravenous bolus of benzodiazepine (which acts through GABA mediation) that would have been effective if given early loses its effectiveness at later stages. In breaking the cycle of seizures with anesthetic sedation, the hope is that the GABA changes reverse sufficiently for normal inhibitory mechanisms to resume.

A number of additional treatments should be considered at this stage. 9 Foremost is resective epilepsy surgery, which can be life-saving. 10 However, surgery can only be contemplated if a definite focus is identified, and can be removed without producing unacceptable neurological deficit. Having a consistent EEG localization of seizures and a concordant MRI lesion is vital in this regard; a decision to operate is made easier if the putative focus is in the nondominant hemisphere, or distant from...
It is Day 18 on ICU. The regional epilepsy team excludes resective surgery as a realistic option. Having failed a trial of IV ketamine, the patient remains in pentobarbital coma in addition to three anticonvulsants and the ketogenic diet. The family asks for a prognosis.

Few physicians would disagree on the general principal that the longer any critical illness persists, the worse the eventual outcome, and the requirements of ICU care carry their own hazards which may threaten life—infections, deep vein thromboses, critical illness polyneuropathy, etc. Most patients with prolonged SE do not recover to their baseline, and many are left with major neurological sequelae. Nevertheless, families should be informed that it is not uncommon for patients to recover to a surprisingly good extent, even with a protracted course: ‘... especially in status epilepticus where no cause is found ... the neurologist has a role in the intensive care situation in insisting that therapy is continued to ensure that premature withdrawal of care is not contemplated.’

The medical student finishes his rotation and asks for take-home messages.

SE is a life-threatening condition; refractory SE carries a high mortality, and among those who recover, <20 percent approach their pre-morbid level of function. Early recognition of SE is vital: delays in instituting aggressive and appropriate treatment significantly deter later attempts to halt the cascade of more seizures and excitotoxic brain damage. Do everything to find a cause for the patient’s syndrome; treating the underlying disease does far more to improve outcome than mere suppression of seizures. Seek expert help if SE persists beyond the first few withdrawals of sedation: the patient may benefit from emergency brain surgery or other ancillary treatments. In a patient with a protracted course, be realistic about eventual functional outcome with the family, but also do not lose hope.

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