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Short communication

Plasma exchange in cryptogenic new onset refractory status epilepticus

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ABSTRACT

Objective: New onset refractory status epilepticus (NORSE) is a recently described entity and has been difficult to treat because the etiology is often cryptogenic. Our aim in each case was to stop status epilepticus while simultaneously searching for the etiology.
Methods: We describe three patients who presented with NORSE, who were refractory to multiple anticonvulsants and general anesthetics for at least 5 days. All patients had an extensive evaluation including MRI brain, CSF studies, radiologic scans for malignancy and serological autoimmune and infectious investigations.
Results: Each patient responded dramatically to the use of plasma exchange therapy with cessation of status epilepticus by the fourth day of treatment. Although an etiology was sought after, no appropriate cause for NORSE could be found.
Conclusion: We propose early use of plasma exchange therapy (Class IV evidence) in hopes to prevent the complications of status epilepticus and prolonged hospitalization.

1. Introduction

New onset refractory status epilepticus (NORSE) in adults can be difficult to treat especially in cases where the etiology remains unknown, despite extensive evaluation including autoimmune, infectious and metabolic studies.[1] These patients present a therapeutic challenge because outcome is often poor due to prolonged hospitalization. Etiology is often presumed to be viral encephalitis based on MR imaging abnormalities or mild CSF pleocytosis, however, some of these changes may be due to the seizure activity itself.[2,3] We report our experience with 3 patients with NORSE who responded to plasma exchange therapy after multiple anticonvulsants and general anesthetics failed. While much is still unknown about this disease entity, our experience suggests that immune therapies should be considered early on in the hospital course to prevent high morbidity and mortality.

2. Case reports

2.1. Patient 1

A 43-year-old African-American woman with no prior history of seizures and no risk factors for epilepsy presented with her first generalized tonic–clonic seizure and a preceding flu-like illness. Initial EEG showed background slowing and a brain MRI was normal. She was discharged home with phenytoin, but developed progressive confusion over the next 3 days and was readmitted. A stat EEG showed bitemporal independent focal seizures. She was initiated on fosphenytoin and levetiracetam intravenously. Her CSF analysis, MRI brain and laboratory data are shown in Table 1 and Fig. 1B. The MRI showed bilateral hippocampal hyperintensities, suspicious for limbic encephalitis. Her continuous EEG (cEEG) monitoring showed approximately 2 seizures/h originating from bilateral temporal lobes lasting 30–90 s (Fig. 1A). Given no improvement in seizures on EEG, she was treated with phenobarbital, then propofol infusion and was finally placed in a pentobarbital coma to achieve burst suppression of EEG activity for 48 h. Seizures returned promptly when pentobarbital was lightened and so the barbiturate coma was repeated again for 96 h. A trial of methylprednisolone 1 g daily for 3 days was given simultaneously with no improvement and seizures resumed as pentobarbital was withdrawn. On day 18 of hospitalization, plasma exchange (PE) therapy was instituted for 5 days, as she remained on a midazolam infusion. On the fourth day of treatment, her EEG began to improve with resolution of seizures and the

Abbreviations: NORSE, new onset refractory status epilepticus; cEEG, continuous EEG; PE, plasma exchange; HC, hippocampal.

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Table 1
Comparison of presentation, investigations and treatment among 3 patients.

Patient	1	2	3
Initial EEG	Independent bilateral partial-onset seizures	Right temporal lobe seizures	Generalized seizures
MRI brain	Bilateral hippocampal (HC) hyperintensities	Bilateral HC hyperintensities, greater on the right	Bilateral HC hyperintensities
Maximally abnormal CSF	WBC: 62 (98% L) Protein: 29.7 mg/dl Glucose: 57 mg/dl	WBC: 0 Protein: 43.6 mg/dl Glucose: 149 mg/dl[a]	WBC: 9 (20% N, 69% L, 11% M) Protein: 37.9 mg/dl Glucose: 72 mg/dl
Infectious[b]	Negative	Negative	Serum *Mycoplasma pneumoniae* IgM positive[c]
Paraneoplastic panel[d] Other imaging for evaluation of malignancy	Negative including anti-VGKC antibody (Ab), CT chest, abdomen, pelvis	Negative including anti-VGKC Ab, CT chest, abdomen, pelvis, testicular US	Negative including anti-NMDAR Ab and anti-VGKC Ab, CT chest, abdomen, MRI pelvis
Antiepileptics used in sequence	Fosphenytoin, levetiracetam, phenobarbital	Carbamazepine, fosphenytoin, levetiracetam, lacosamide	Fosphenytoin, levetiracetam, lacosamide, valproic acid, phenobarbital, lorazepam
Continuous IV anesthetics used	Pentobarbital, midazolam	None	Propofol, pentobarbital, ketamine, midazolam, lorazepam
Overall outcome	Mild impaired memory, rare seizures	Moderate impaired memory, partial complex seizures	Death secondary to bowel necrosis and hospice status

[a] Patient 2 had uncontrolled type 2 diabetes mellitus.
[b] Infectious studies done in all 3 patients included testing for cryptococcus, Coccidioides immitis, HSV types 1 and 2, VZV, CMV, EBV, WNV, enteroviruses, arboviruses, TB, VDRL, bacterial and fungal cultures in CSF and serum.
[c] A repeat test 13 days later showed titers were negative for IgM and positive for IgG, however, Mycoplasma was never detected in the CSF by PCR or in respiratory cultures, cold agglutinins and chest radiograph were also negative.
[d] Antibodies to the following: ANNA-1, -2, -3, PCA-1, -2, PCA-Tr, Amphiphysin, CRMP-5 IgG, striational muscle, P/Q type voltage gated calcium channel, N-type voltage gated calcium channel, Ach receptor binding, Ach ganglionic neuronal, glial nucleus. The first patient had an earlier paraneoplastic panel from 2009 which tested antibodies to the following: ANNA-1, -2, anti-neutrophil, Purkinje screen, potassium gate MPO, serine protease. L, lymphocyte; N, neutrophil; M, macrophage; anti-VGKC Ab, anti-voltage-gated potassium channel; anti-NMDAR, anti-NMDA receptor.

midazolam infusion was gradually tapered along with phenobarbital and phenytoin. She did not have any further seizures and was discharged 1 week later. She went to acute rehabilitation on 2 anticonvulsants, valproic acid and levetiracetam. At follow-up, she has partial complex seizures characterized by staring and confusion twice a month. Her MRI brain one year later showed resolution of hippocampal hyperintensities.

2.2. Patient 2

A 51-year-old Hispanic male initially presented with a febrile illness and a suspected complex partial seizure. However, he had normal CSF findings and routine EEG. He was started on carbamazepine, but stopped the medication 2 weeks later on his own. Four months later, he returned with a 5-day history of confusion and lethargy. His CSF, MRI and laboratory evaluation are shown in Table 1 and Fig. 1C. An initial EEG showed intermittent focal seizures emanating from the right temporal region lasting from 20 to 120 s interspersed by a background of mild diffuse slowing. Initial MRI of the brain showed hyperintensities in bilateral hippocampi with subtle enhancement noted on the right. He was placed on cEEG monitoring and treated with fosphenytoin followed by levetiracetam and lacosamide, however, there was no improvement in mental status. On day 5 of hospitalization, plasma exchange was instituted for 5 days as he was maintained on the above anticonvulsants. After completing plasma exchange, antiepileptic medication was gradually weaned and seizures did not recur. Eventually, he was discharged on 2 anticonvulsants, phenytoin and lacosamide. At 6-month follow-up, he has recovered well, though he reports short-term memory loss and inability to return to work.

2.3. Patient 3

A 39-year-old previously healthy Caucasian/African-American woman presented with a flu-like illness 5 days prior to her first generalized tonic–clonic seizure. She was lethargic and confused at presentation. An initial EEG showed multiple bilateral independent seizures clinically characterized by eye blinking. She was initially treated with lorazepam followed by fosphenytoin and levetiracetam. A cEEG showed non-convulsive status epilepticus with bilateral periodic discharges at 2–3 Hz interspersed by brief electrographic seizures lasting 60–120 s. A propofol infusion initially suppressed seizures, but they returned promptly during weaning. Valproic acid and lacosamide were added, but did not improve SE. She was then placed in a pentobarbital coma on day 10. CSF, serological studies and brain MRI data are shown in Table 1 and Fig. 1D. She had serial brain MRIs which showed increasingly hyperintense hippocampal changes. Each time the pentobarbital infusion was decreased, bilateral independent periodic discharges along with intermittent independent bilateral focal seizures returned. During the second week, a 5-day course of intravenous immunoglobulin therapy followed by 5 days of high dose methylprednisolone did not improve her status. She developed an acute abdomen and at emergent laparotomy, was found to have severe bowel infarction. This was presumably due to prolonged use of vasopressors and nearly 90% of her bowels were resected. After surgery, given no improvement on EEG, other anesthetics including ketamine, midazolam and lorazepam infusions were attempted, but she continued to have seizures while on maximal doses of each of these agents. On day 29 of hospitalization, PE was instituted for 5 days. With simultaneous weaning of anesthetic infusions, she began opening her eyes spontaneously to voice and follow some commands. Her EEG showed diffuse slowing with frequent epileptiform discharges during sleep, but no further seizures. She was weaned off of all anesthetic agents and her seizures were controlled with oral lorazepam, phenobarbital, levetiracetam and lacosamide. However, her bowel condition deteriorated and she was eventually sent to hospice where she died quickly from respiratory failure. At autopsy, she was found to have necrotic bowel proximal to her ostomy site along with nonspecific inflammation of bilateral hippocampi.