Partial Status Epilepticus with Paradoxical Protein-Cytologic Dissociation in Cerebrospinal Fluid

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Int J of Ep:2020;6:59–64

Abstract

Status epilepticus is associated with high morbidity and mortality, often requiring multiple drug interventions and intensive care monitoring. Etiology of status epilepticus plays a crucial role in the treatment, natural course and outcome of the patient, prompting extensive testing and imaging. For example, an important risk for status epilepticus in adults and children is the presence of an underlying viral or bacterial central nervous system infection, appropriate treatment of which can improve the outcome of the patient. We present three cases of new-onset refractory status epilepticus in women who did not have evidence of a central nervous system infection and had significantly elevated leukocytes compared to protein in the cerebrospinal fluid. This finding suggests an autoimmune etiology; however, standard autoimmune testing was unremarkable in all cases. This case series highlights the variability in presentation and clinical course in patients presenting with status epilepticus of unknown cause, and we discuss the importance of further research into appropriate and reliable diagnostic evaluations.

Keywords
- autoimmune encephalitis
- new-onset refractory status epilepticus
- NORSE
- paraneoplastic syndrome
- partial status epilepticus

Introduction

New-onset refractory status epilepticus (NORSE) is a life-threatening emergency requiring treatment with antiepileptic medications, often including sedation and identification of underlying etiologies to prevent recurrence. Patients often undergo extensive diagnostic testing, including brain imaging and cerebrospinal fluid (CSF) testing, to identify etiologies and adjust treatment plans accordingly. We report three cases at two institutions with similar presentations and laboratory test results. All patients were female and presented with status epilepticus of uncertain etiology. All their CSF tests revealed disproportionately higher white blood cell counts than protein levels, without evidence of infections. These findings suggested viral or autoimmune etiologies, although standard CSF viral encephalitis and autoimmune panels were unremarkable. We explore these case findings and what they suggest for further research into underlying etiologies.

Case Reports

Case 1

A 10-year-old girl with no medical conditions experienced upper respiratory infection symptoms without fever, and 4 days later developed abnormal gait and urinary incontinence. For the next 3 days, she experienced lethargy, aphasia, and left-sided weakness, and was brought to the hospital, where she became febrile (38.2°C) and less alert. She experienced two witnessed generalized tonic–clonic seizures with rightward eye deviation, which progressed to generalized convulsive status epilepticus. Empiric acyclovir and antibiotics were started, but later stopped when CSF studies showed no viral or bacterial infections. A continuous electroencephalogram (EEG) initially showed persistent focal-onset seizures with impaired awareness seizures at multiple sites. She was treated with levetiracetam, fosphenytoin, phenobarbital, perampanel, lacosamide, and midazolam, ketamine, and pentobarbital drips. Her

DOI https://doi.org/10.1055/s-0040-1716432
ISSN 2213-6320.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

seizures transiently remitted into a burst suppression pattern on EEG only with pentobarbital, and reemerged when pentobarbital was weaned, despite the presence of other medications. She was also treated with plasmapheresis, intravenous immunoglobulin, rituximab, and two courses of intravenous methylprednisolone for presumed autoimmune etiology.

The patient's CSF showed elevated white blood cell count of 111 per cm^3, with lymphocytic predominance (73%), normal neutrophils (16%), mildly elevated protein level (46 mg/dL), and normal glucose level (69 mg/dL). Viral and bacterial cultures, and immunoglobulin G (IgG), myelin basic protein, and oligoclonal bands levels were all negative. Additional CSF encephalitis and autoimmune panels (testing for antibodies against HSV-1, HSV-2, measles, mumps, Varicella-Zoster virus, West Nile virus, IgG/IgM, N-methyl-D-aspartate (NMDA) receptor VGKC, GAD65, γ-amino butyric acid-B (GABA-B) receptor, AMPA-R, ANNA-1/2/3, AGNA1, PCA-1/2/Tr, amphiphysin, CRMP-5 IgG, LGI1 IgG, and CASPR2 IgG antibodies) were all negative. Serum anti-GAD65 level was slightly elevated at 0.05 nmol/L, although this has a low positive predictive value for neurological autoimmunity. A magnetic resonance imaging (MRI) brain revealed ill-defined T2/FLAIR (fluid-attenuated inversion recovery) hyperintensities at the right frontal, right temporal, and left cerebellar gray-white matter junctions (►**Fig. 1**). Serum studies for thyroid hormone, hepatitis B surface antigen, IgG, and a serum autoimmune panel (testing for ANA, acetylcholine receptor binding and ganglionic neuronal, CCP, CASPR2 IgG, LGI1 IgG, NMO, AMPA-R, GABA-B receptor, VGKC, ANNA-1/2/3, AGNA-1, PCA-1/2/Tr, amphiphysin, N-type calcium channel, P/Q type calcium channel, NMDA receptor, and CRMP-5 IgG antibodies) were negative. A subsequent MRI brain revealed additional bilateral cortical and subcortical T2/FLAIR hyperintensities, new microhemorrhages, and increased ventricular size.The patient suffered acute respiratory distress syndrome, metabolic acidosis, and wide-complex tachycardia, culminating in two cardiac arrests, renal failure, hepatic failure, and disseminated intravascular coagulopathy. Care was withdrawn per family wishes, and after she passed away, brain autopsy revealed reactive gliosis and degeneration, while indirect immunostaining of brain tissue with the patient's own CSF yielded a positive result. These findings were consistent with autoimmune encephalitis and the resultant status epilepticus.

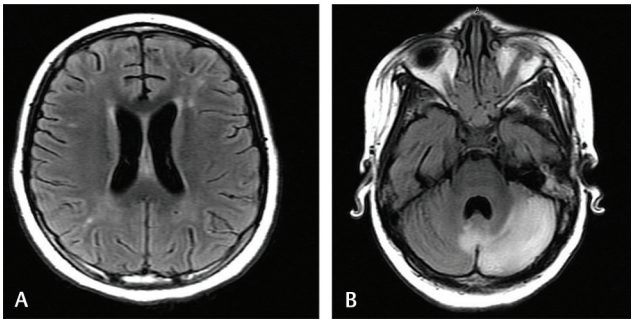

Fig. 1 Magnetic resonance imaging brain fluid-attenuated inversion recovery sequences for Case 1, showing ill-defined hyperintensities in the (**A**) right temporal and (**B**) left cerebellar gray-white matter junctions.

Case 2

A 24-year-old right-handed woman with hypertension and membranoproliferative glomerulonephritis type 1A experienced headache, dizziness, and emesis, and 3 days later became unresponsive with urinary incontinence and left face and arm jerking episodes. When brought to the hospital, she was alert and interactive, but had difficulty naming objects and repeating sentences. She subsequently had intermittent nonsuppressible left-sided facial twitching episodes, with EEG revealing nearly continuous right central focal onset seizures (►**Fig. 2**), and later independent left central focal onset seizures (►**Fig. 3**). An MRI brain revealed a left inferior frontal gyrus nonenhancing T2/FLAIR hyperintensity, and another MRI brain revealed additional T2/FLAIR hyperintensities in the right parietal lobe, temporal gyrus, and posterior insula (►**Fig. 4**).

The patient was treated with intermittent lorazepam, then levetiracetam, lacosamide, phenytoin, valproic acid, and propofol, midazolam, ketamine, and pentobarbital drips. Despite receiving these, she only achieved a burst suppression pattern on EEG for 6 hours while on pentobarbital (►**Fig. 5**). She was also treated with plasmapheresis, intravenous immunoglobulin, and intravenous methylprednisolone for a presumed autoimmune etiology.

She had two lumbar punctures, the first before autoimmune treatments and the second after completing an intravenous immunoglobulin course. The first sample showed an

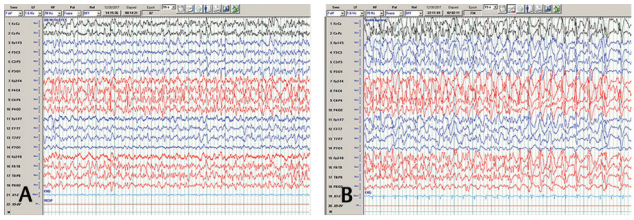

Fig. 2 Continuous electroencephalogram segments for Case 2, showing a right central focus for seizures, associated with left facial twitching. Seizures are centered at the (**A**) C4 electrode, and later the (**B**) C4 and F8 electrodes.

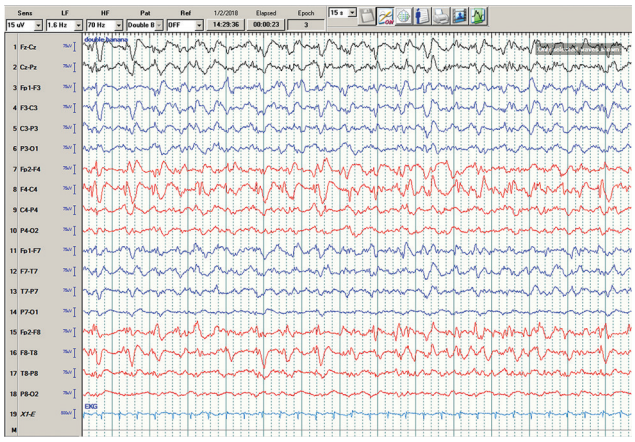

Fig. 3 Continuous electroencephalogram segment for Case 2, showing a left frontal focus centered at electrode F3, independent of right central focal onset seizures.

elevated white blood cell count (110 cm^3), lymphocytic predominance (58%), mildly elevated protein level (46 mg/dL), and normal glucose level (64 mg/dL). The second sample also showed elevated white blood cell count (91 cm^3), but higher lymphocytic predominance (86%), protein level (160 mg/dL), and glucose level (134 mg/dL). Viral and bacterial encephalitis panels were negative in the first CSF sample, as were IgG and oligoclonal band levels, and cytology. A CSF autoimmune panel, testing for similar antibodies as in Case 1, was also negative. Serum studies for C-reactive protein, erythrocyte sedimentation rate, Lyme antibody, hepatitis panel, RPR, HIV, chlamydia, gonorrhea, and an autoimmune panel (testing for ANA, ANCA, ACE, rheumatoid factor, and the following antibodies: antiglomerular, anti-SSA/SSB, anti-dsDNA, anti-TPO, and anti-Hu/Ri/Yo antibodies) were also negative.

Per the patient's family's request, she was transferred to another hospital, where status epilepticus resolved after a few days despite no significant medication changes, indicating cerebral function decline. She continued to have decreased level of consciousness after partial status epilepticus resolved, and ultimately care was withdrawn.

Case 3

A 58-year-old right-handed woman with secondary progressive multiple sclerosis (MS) complicated by autonomic dysfunction, and no previous seizures, suffered a generalized convulsion, loss of consciousness, and urinary incontinence. When brought to the hospital, she had leftward head and eye version with bilateral arm jerking episodes. Continuous EEG revealed left frontal focal aware status epilepticus associated with right arm jerking. A computed tomography head revealed juxtacortical and periventricular white matter changes consistent with the patient's known distribution of lesions, with no new lesions to trigger status epilepticus. Two MRI brain studies revealed additional T2/FLAIR hyperintensities in the bilateral hippocampi, left thalamus, and left caudate nucleus (►**Fig. 6**), and left hemispheric cortical diffusion restriction on diffusion-weighted imaging sequences (►**Fig. 7**).

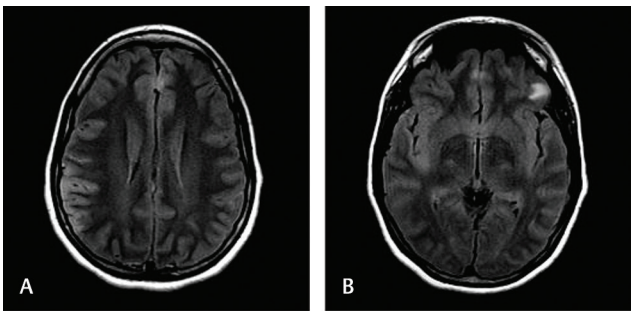

Fig. 4 Second magnetic resonance imaging brain fluid-attenuated inversion recovery (FLAIR) sequences for Case 2, showing nonenhancing FLAIR hyperintensities in the (**A**) right parietal lobe and (**B**) left inferior frontal lobe.

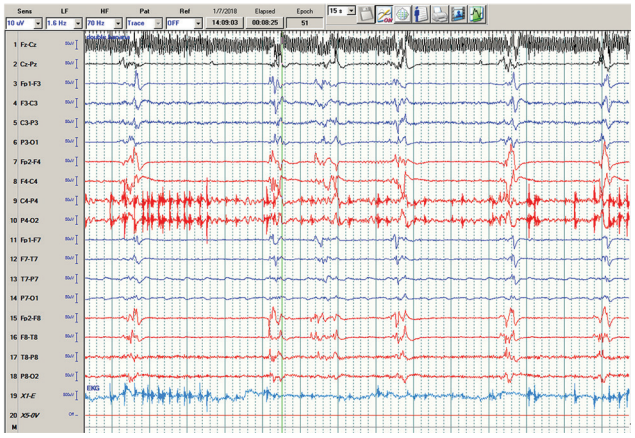

Fig. 5 Continuous electroencephalogram segment for Case 2 showing burst suppression pattern, with bursts showing bilateral seizure activity.

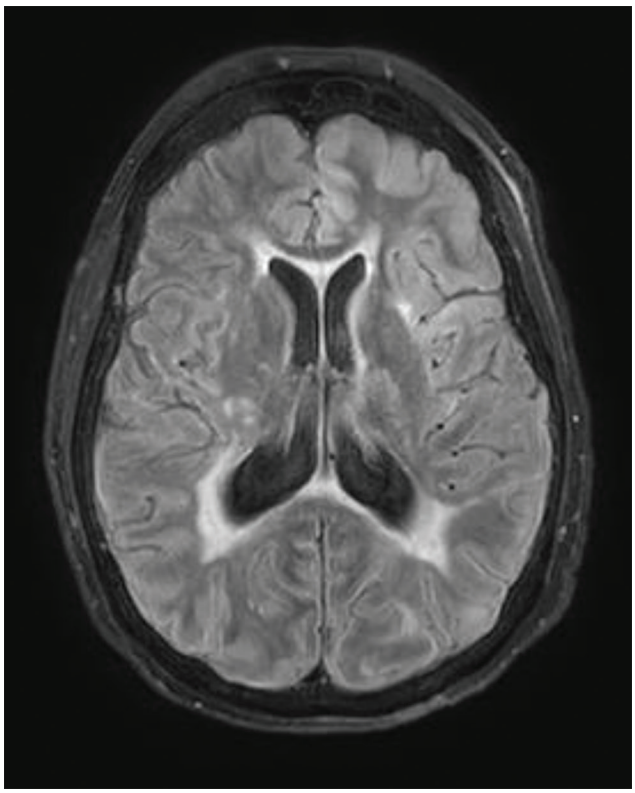

Fig. 6 Magnetic resonance imaging brain, T2/fluid-attenuated inversion recovery sequence, for Case 3, showing hyperintensities involving the left thalamus, left caudate nucleus, and bilateral hippocampi, which do not respect vascular boundaries.

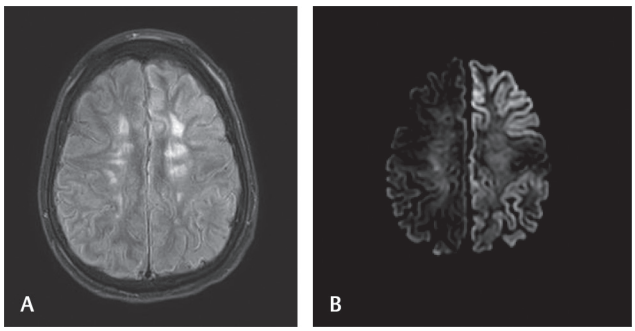

Fig. 7 Magnetic resonance imaging brain for Case 3, showing (**A**) bilateral subcortical hyperintensities on fluid-attenuated inversion recovery sequence and (**B**) left cortical diffusion restriction on diffusion-weighted imaging sequence.

The patient was treated with intermittent lorazepam and midazolam, then levetiracetam, valproic acid, lacosamide, and midazolam and propofol drips. Focal aware status epilepticus resolved with combined levetiracetam and lacosamide once the drips were weaned off. Her disease-modifying agent for MS, dalfampridine, known for lowering seizure threshold, was replaced with teriflunomide.

The patient's CSF showed elevated white blood cell count (183 cm^3), neutrophil predominance (91%), low lymphocyte count (3%), mildly elevated protein (47 mg/dL), and normal glucose (86 mg/dL). Serum viral, bacterial, and fungal cultures, and CSF viral and bacterial encephalitis panels, were negative. Cytology, paraneoplastic panel, and levels for myelin basic protein and oligoclonal bands in CSF were also negative. Serum studies included a viral panel, positive for HSV-1 IgG antibody, indicating only previous exposure, and were negative for hepatitis A, B, and C viruses, HSV-2 IgG, influenza A, JC virus, respiratory syncytial virus, and West Nile virus. A serum autoimmune panel (testing for ANA, c-ANCA, pANCA, rheumatoid factor, anti-dsDNA antibody, and anti-SSA/SSB antibodies) was also negative.

A lumbar puncture after status epilepticus resolved showed no remaining white blood cells, and normal protein and glucose levels. The patient required tracheostomy and feeding tube and was discharged to an inpatient rehabilitation center.

Discussion

The three female patients described in these case studies presented with NORSE with focal onset but no previous history of epilepsy. Each had abnormal CSF studies, characterized by pleocytosis out of proportion to mildly elevated protein. Definitive etiologies were not identified by extensive CSF testing.

The entity of NORSE was first characterized in 2005 to describe patients presenting for the first time with a prolonged epileptic seizure, or a cluster of seizures without a return to baseline in between them.[1] This effects patients at all ages, but more commonly children and young adults.[1] Although half of all presentations of NORSE are cryptogenic, the majority of cases with known etiologies are the result of autoimmune encephalitis.[1] This can lead to a comatose state, while the patient undergoes initial workup and treatment.[2]

The workup for status epilepticus includes thorough evaluations for metabolic, infectious, toxic, and cerebral structural etiologies. ►**Table 1** compares the MRI brain, EEG, and CSF findings that can be seen with the various etiologies of encephalitis. In one study, 44% of the patients were antibody-negative, although clinical courses were typical for autoimmune encephalitides.[3] In another study, fever preceded NORSE in 91% of cases.[2] Several MRI abnormalities can be seen but are often nonspecific for etiology. Restricted diffusion may be seen in mesial temporal lobes, and signal hyperintensities may be seen in the hippocampus, cerebellum, cerebral cortex, insula, basal ganglia, brainstem, and even spinal cord.[4,5] In cases of NORSE, there can be symmetric hyperintensities on T2 sequences.[2] Lesions may appear demyelinating without enhancement, similar to acute disseminated encephalomyelitis.[6]

The EEG findings can also be nonspecific, showing lateralized periodic discharges, although delta brushes are more specific for NMDA encephalitis.[5-7] The CSF often yields a moderately elevated lymphocytic pleocytosis, fewer than 100 per mL[5,8] and can show elevated oligoclonal bands or cytoalbuminemic dissociation, although these are not specific for particular etiologies.[4] One study of a NORSE model in rats revealed indirect immunofluorescence positive signals in the cytoplasm and nucleus of hippocampal neurons, suggesting an autoimmune etiology.[9]

Nearly half of adults who present with status epilepticus have no history of epilepsy, indicating possible acute etiologies.[10] Focal etiologies, including structural abnormalities like vascular malformations, posttraumatic gliosis, or inflammatory lesions, are considered in partial status epilepticus presentations.[11] Congenital malformations, including focal cortical dysplasia, are often seen not only during childhood but also in 1.9% of new adult cases.[10] While epilepsy has a prevalence of 2 to 3% in patients with MS,[12] the seizures in the patient in Case 3 were considered unlikely to be related to MS given the absence of new plaques. Although dalfampridine is known to lower seizure threshold, this was unlikely to be a trigger given the patient's tolerance of the medication without seizures for many years prior to this presentation.

Central nervous system (CNS) neoplasms and paraneoplastic syndromes can also cause seizures. Although CSF cytology and immunochemistry are considered the most useful tests to detect CNS neoplasms, they have a combined sensitivity of only 41.3%.[13] Paraneoplastic syndromes, in contrast, can have abnormal CSF in 93% of cases,[13] although these abnormalities include abnormal paraneoplastic panels, protein electrophoresis, or oligoclonal band levels. One study found that CSF oligoclonal bands were found in 63% of paraneoplastic syndromes, and were the only abnormalities in 10% of them.[13] In the same study, hyperproteinorachia (elevated CSF protein) was found within 3 months of a paraneoplastic syndrome diagnosis in 47% of cases, and after 3 months in 28% of cases.[13] This suggests possible subacute inflammation in paraneoplastic syndromes.[13]

Autoimmune encephalitides are rare but can cause significant disease. Antibodies can cross-react with various components of neurons, including gamma-amino butyric acid-B and NMDA receptors, resulting in limbic encephalitis.[14] These can present with seizures, autonomic dysfunction, and behavioral changes.[4] Flow cytometry has been used to evaluate CSF in suspected autoimmune encephalitis cases, and has yielded positive results in cases in which patients have coexisting autoimmune or inflammatory disorders, such as systemic lupus erythematosus or MS.[15] In such cases, flow cytometry typically reveals a high CD4/CD8 ratio.[15] This technique has also been helpful in identifying Rasmussen encephalitis and paraneoplastic encephalitis.[15]

Since these cases did not identify definitive etiologies, they were termed cryptogenic status epilepticus, which one study found represented 54% of all status epilepticus cases.[1]

Table 1 Comparison of MRI brain, EEG, and CSF findings that can be seen in the various pathological etiologies for encephalitis

Pathology	MRI				EEG	CSF
	T2/FLAIR	DWI	Contrast	Perfusion		
Infectious	CSF space hyperintensity	Restricted diffusion	Primarily meningeal enhancement	Decreased blood volume and blood flow	Lateralized periodic discharges	Elevated cell count and protein
					Spike-and-wave discharges	Positive viral PCR or bacterial/fungal culture
Neoplastic	Cortical hyperintensities	No restricted diffusion	Primarily parenchymal enhancement	Increased blood volume and blood flow	Lateralized periodic discharges	Positive cytology/flow cytometry
					Focal slowing	Elevated protein, abnormal protein electrophoresis
						Abnormal paraneoplastic panel
						Oligoclonal bands
Autoimmune	Symmetric hyperintensities	Restricted diffusion	No enhancement	Increased blood volume and blood flow	Lateralized periodic discharges	Moderately elevated lymphocytes
					Delta brushes (NMDA)	Cytoalbuminemic dissociation
						Oligoclonal bands
FIRES	Usually normal in acute phase	Diffuse cytotoxic edema	No enhancement	Increased blood volume and blood flow	Generalized slow waves	Elevated cytokines and chemokines
	Hyperintensities at b/l temporal lobes, basal ganglia, thalami, and brainstem					
	Diffuse cytotoxic edema					
Mitochondrial	Global delayed myelination	Multifocal restricted diffusion	Varying degrees of parenchymal enhancement	Increased blood volume and blood flow	Multifocal discharges	Elevated lactate
	Cystic lesions				Generalized slow waves	Elevated protein

Abbreviations: CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalogram; FIRES, febrile infection-related epilepsy syndrome; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; PCR, polymerase chain reaction.

Cryptogenic status epilepticus could represent a manifestation of autoimmune encephalitides, suggesting the presence of autoantibodies not yet identified and contributing to extensive testing for such individuals.[16]

Conclusion

The differential diagnosis of acute-onset NORSE is extensive. Initial investigations, specifically CSF studies, often aid in identifying etiologies. These cases show varying MRI abnormalities but a consistent CSF pattern of pleocytosis with mild hyperproteinorachia, without infection. While this protein-cytologic dissociation may be seen with CSF draws early in the disease course, these findings may also indicate autoimmune or viral etiologies despite no identified CSF autoantibodies, and may suggest the presence of currently unidentified autoantibodies. This underscores the need for further research into autoimmune and viral etiologies, and empiric immunomodulatory treatment, for cryptogenic status epilepticus.

Conflict of Interest
None declared.

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