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Treatment responsive GABA(B)-receptor limbic encephalitis presenting as new-onset super-refractory status epilepticus (NORSE) in a deployed U.S. soldier

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ABSTRACT – A 23-year-old, previously healthy, deployed U.S. soldier presented with bilateral temporal lobe seizures recalcitrant to multiple antiepileptic drugs and anti-seizure anaesthetic agents. He received methylprednisolone, intravenous immunoglobulins, plasma exchange, and rituximab for presumed autoimmune encephalitis before achieving seizure freedom. Six weeks after presentation, the aetiology of his refractory seizures was found to be due to autoantibodies targeting the anti-GABA(B)-receptor. This case is noteworthy for being the first reported case of anti-GABA(B)-receptor limbic encephalitis presenting with new-onset refractory status epilepticus (NORSE), a clinical syndrome that often carries a grave prognosis and in which a treatable aetiology is often never discovered. Our case also supports testing for GABA-receptor autoantibodies and the upfront use of multi-modal immunotherapy in patients presenting with limbic encephalitis and new refractory seizures.

Key words: all epilepsy/seizures, status epilepticus, encephalitis, GABA(B)-receptor, new-onset refractory status epilepticus (NORSE)

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New-onset refractory status epilepticus (NORSE) is a syndrome of prolonged seizure state occurring *de novo* in previously healthy patients. It generally carries a grave prognosis and the underlying cause often goes undiscovered. We report the clinical features,

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management, and remarkable recovery of a deployed U.S. soldier with anti-GABA(B) limbic encephalitis, presenting as NORSE.

Case study

While deployed in Afghanistan, a previously healthy 24-year-old soldier had a generalized tonic-clonic seizure (GTCS) and was evacuated to Landstuhl Regional Medical Center in Germany. Two days later, brain MRI and EEG were normal. The following day, he suffered another GTCS. He was loaded with levetiracetam and evacuated to Walter Reed National Military Medical Center. He developed a progressive neurobehavioural syndrome, including global confusion and confabulation. He continued to have GTCS as well as dyscognitive seizures. EEG showed frequent seizures arising from the bitemporal regions, predominantly left-sided (*figure 1*). He developed near continuous seizures and was transferred to the intensive care unit. Upon arrival to the ICU, CSF revealed 14-16 WBCs with lymphocytic predominance. Seizure activity persisted despite treatment with multiple antiepileptic medications (levetiracetam, phenytoin, divalproex, lacosamide, and topiramate) and anaesthetic agents (midazolam, propofol, and pentobarbital). Brain MRI revealed mild T2 hyperintensities in the left hippocampus which may represent limbic encephalitis vs. postictal oedema (*figure 2*). Broad-spectrum anti-bacterials and anti-virals were initiated, however, within 1-2 weeks, initial infectious, autoimmune, and malignancy work-ups were unrevealing (*table 1*). Antimicrobial therapy was discontinued and a presumed diagnosis of autoimmune encephalitis was made. His clinical presentation of afebrile limbic encephalitis in the context of a new refractory seizure state prompted additional testing to resolve diagnostic uncertainty. Serum and CSF samples were sent to the Institut d'investigacions biomédiques August Pi I Sunyer in Spain for full autoimmune seizures/status epilepticus screening. At its worst, which was about 1 week into his ICU course, the patient was having generalized electrographic seizures about every five minutes despite anti-seizure anaesthesia.

He was started on IVIG (0.4 g/kg/day for 5 days) and methylprednisolone (1 g/day for 5 days), but continued to have seizure activity, with attempts to wean off anaesthesia. He then received five treatments of plasmapharesis. Further attempts to wean off anaesthesia were followed by breakthrough seizure activity. Four treatments of once weekly rituximab (375 mg/M^2) were given and he was transitioned from pentobarbital to ketamine. His last clinical GTCS was recorded about 2 weeks after rituximab was started, prompting a repeat methylprednisolone course. At around this time, which was 6 weeks after presentation, CSF samples from the Institut d'investigacions biomédiques August Pi I Sunyer returned positive for antibodies targeted against the GABA(B) receptor. After the rituximab course was completed, he was weaned off anaesthetic agents without return of seizures. He showed substantial gradual neurological improvement and at 6 months following presentation, he was independent in all activities of daily living, with normal EEG. He remained with working memory dysfunction that also continued to improve over the ensuing year. Mycophenolatate mofetil (1 g/twice daily) was initiated as maintenance immunosuppressant, and his antiepileptic regimen was slowly reduced to levetiracetam monotherapy. Malignancy surveillance (brain MRI, whole-body PET, thorax CT, and testicular ultrasound) remained unrevealing 12 months after presentation. The patient had no memory of anything 8 months prior to presentation, including his entire 6-month deployment to Afghanistan.

Discussion

This case is noteworthy for being the first reported case of anti-GABA(B)-receptor limbic encephalitis presenting as NORSE, as well as for its favourable outcome.

Refractory status epilepticus (SE) is SE that has not responded to first-line (benzodiazepine) or second-line therapy and requires application of general anaesthesia (Shorvon, 2011). Super-refractory status epilepticus is a stage of refractory SE characterized by SE, continuing or recurring 24 hours or more after the onset of anaesthesia, including withdrawal/reduction of anaesthesia (Shorvon, 2011). It is encountered typically in two distinct clinical situations: (1) in patients with severe acute brain injury; and (2) in patients with no history of epilepsy in whom SE develops *de novo* (NORSE). Frequently, no distinct aetiology is found and these cases are presumed to be viral in origin. A subset of NORSE patients are increasingly thought to be related to an aberrant immune response targeting neuronal cellular surface antigens (Costello *et al*., 2009).

The clinical spectrum of anti-GABA(B) autoimmune encephalitis includes limbic encephalitis, seizures with or without status epilepticus, ataxia, opsoclonus-myoclonus, and Morvan syndrome (Lancaster *et al*., 2010; Boronat *et al*., 2011; Höftberger *et al*., 2013; Kim *et al*., 2014). It is found to be associated with small cell lung carcinoma in about 50% of cases, usually in older individuals. The brain regions most affected are the hippocampi and the temporal lobes. Pooling from four large case series, 51 patients with anti-GABA(B) encephalitis have been reported, 5 of whom presented with or developed

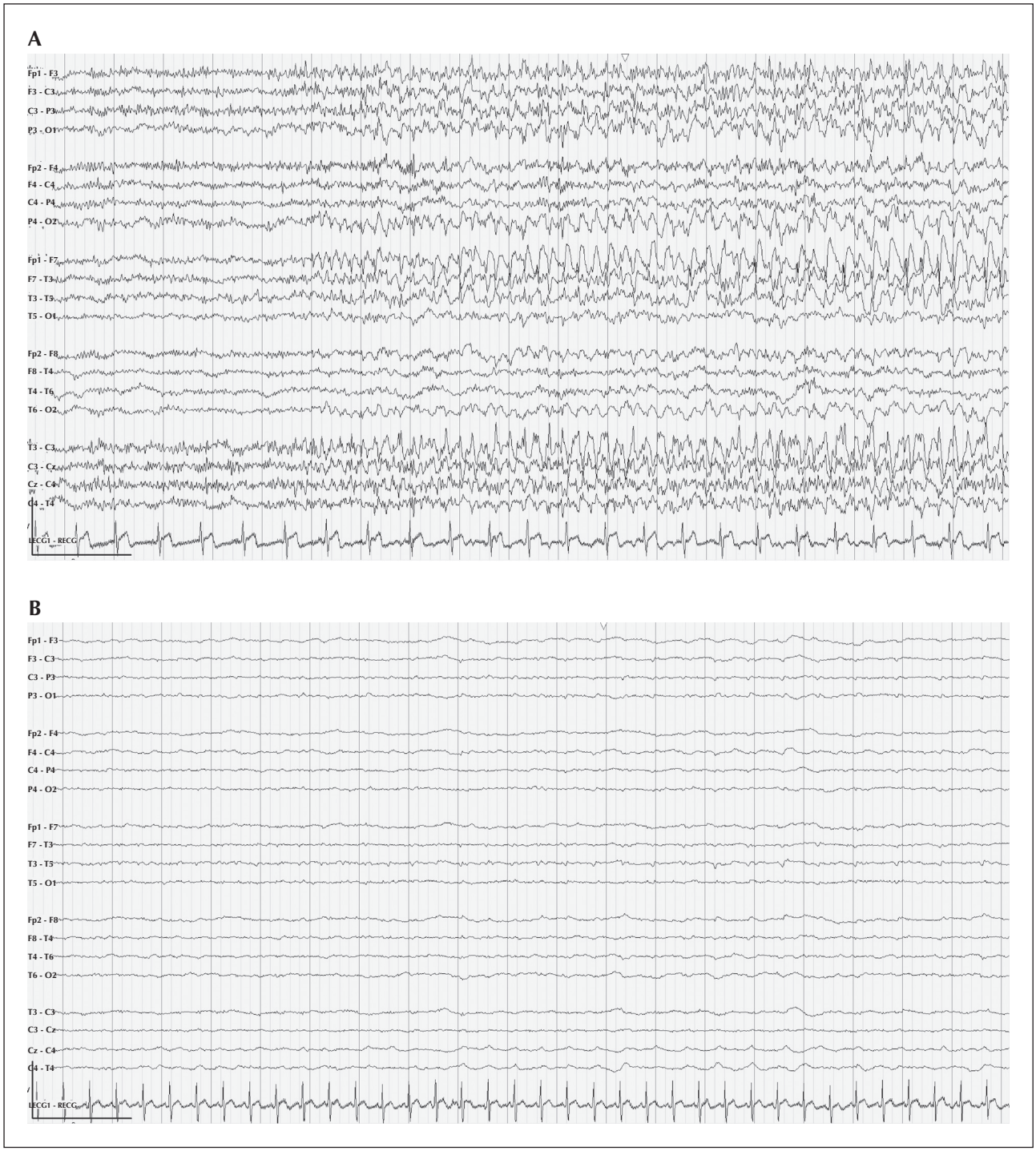

Figure 1. EEG series demonstrating left and right temporal lobe seizures, including during burst suppression.
(A) Day 10 after presentation; 7 uV/mm, 15 mm/sec. Focal left temporal seizure observed 3 days after presentation, while being treated with four AEDs. (B) Day 17 after presentation; 5 uv/mm, 15 mm/sec. Subtle left temporal seizure (T3-T5 lead), despite treatment with 5 AEDs (including propofol and midazolam) and burst suppression.

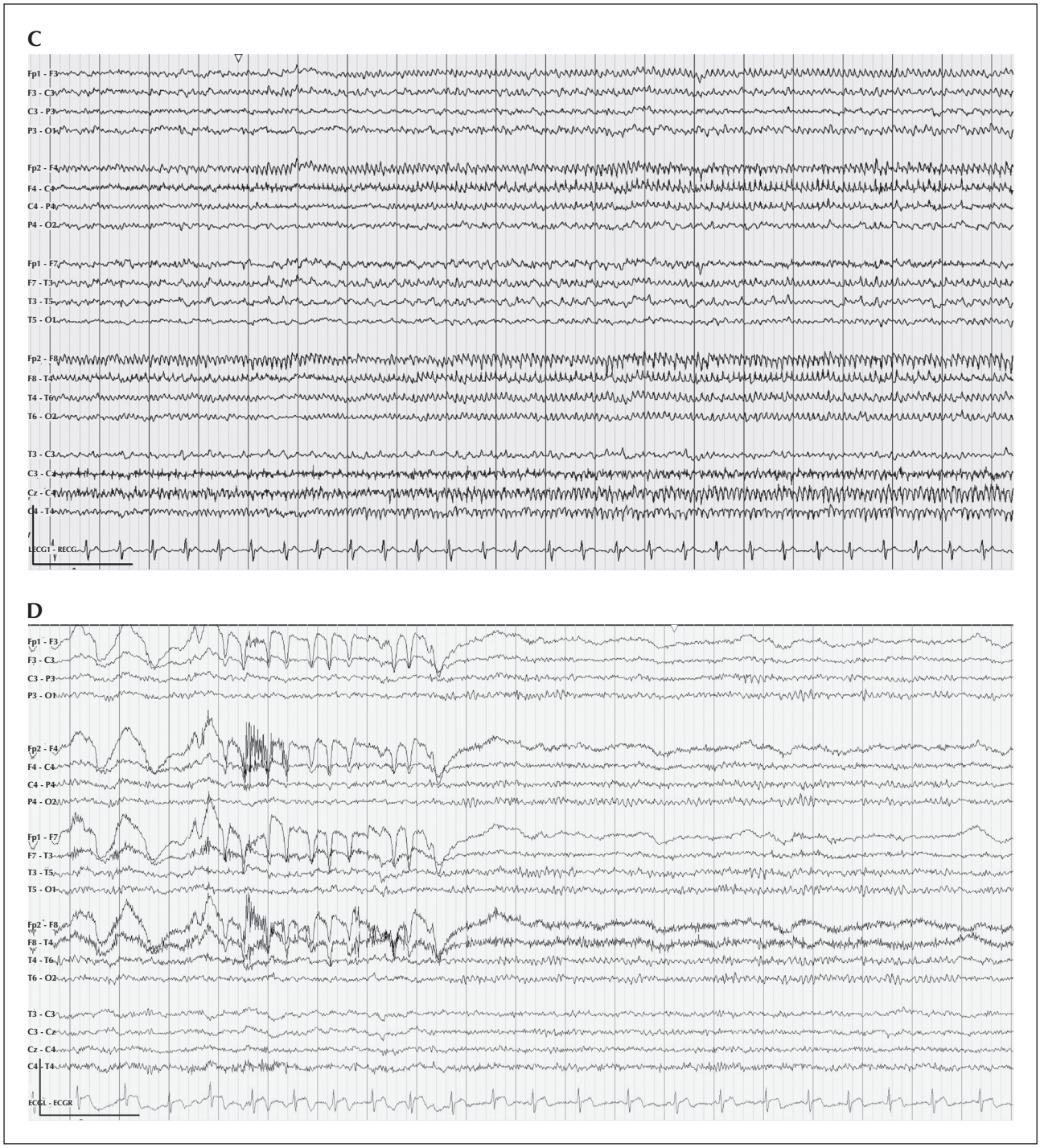

Figure 1. *(Continued)* (C) Day 38 after presentation; 7 uv/mm, 15 mm/sec. Focal right hemispheric seizure observed 4 weeks into the treatment course (IVIG, methylprednisolone, plasmapharesis). (D) Five months after presentation; 7 uv/mm, 15 mm/sec. Normal EEG. Patient received last dose of rituximab 3.5 months prior.

status epilepticus (Lancaster *et al*., 2010; Boronat *et al*., 2011; Höftberger *et al*., 2013). Four died and only one survived with a favourable outcome following plasmapharesis/steroids. A recent observational study described 4 patients presenting with refractory seizures requiring pharmacologically-induced coma who had a high level of CSF and serum GABA(A)-receptor autoantibodies (Petit-Pedrol *et al*., 2014).

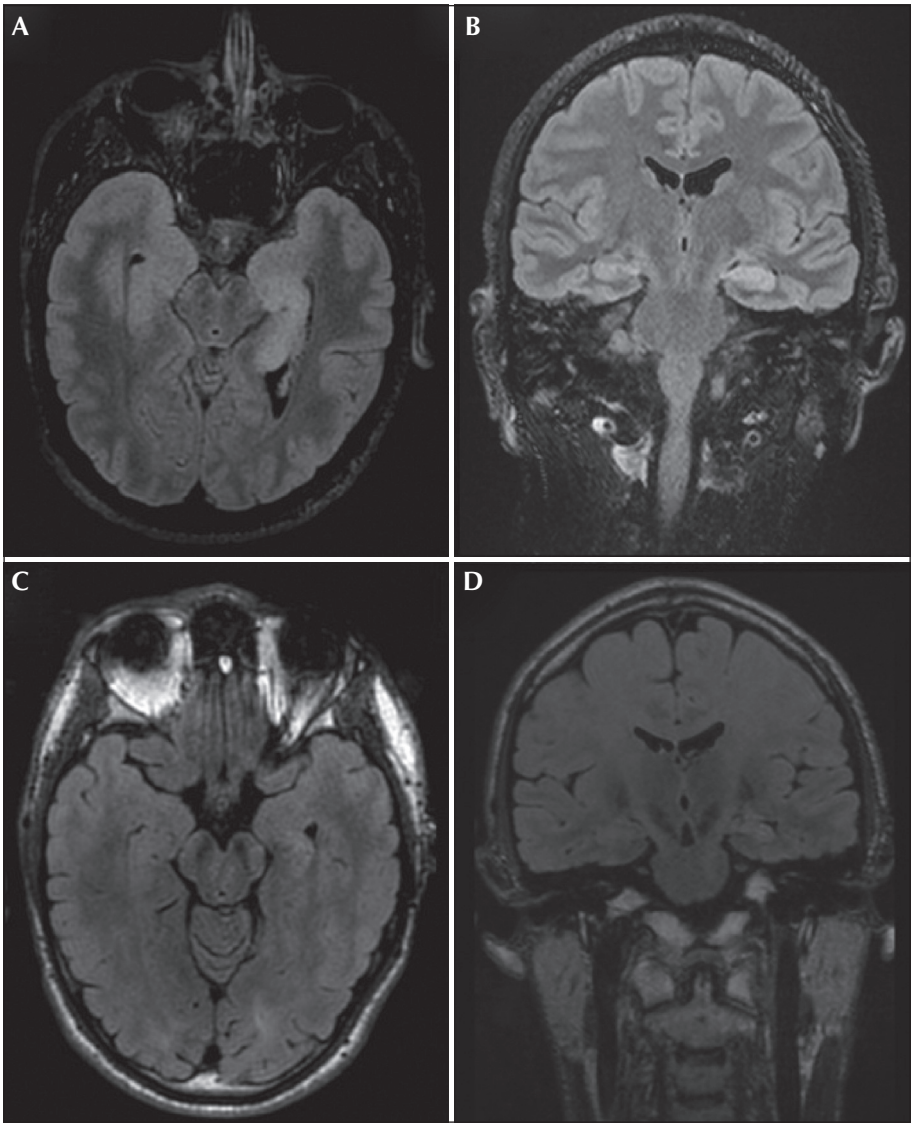

Figure 2. MRI series demonstrating limbic encephalitis and recovery seven months later, using T2-FLAIR brain MRI.
(A) Day 15 after presentation, axial-view. (B) Day 15 after presentation, coronal view. (C) Month 7 after presentation, axial-view. (D) Month 7 after presentation, coronal view.
(A, B) Asymmetric enlargement and T2 hyperintensity of the left more than the right hippocampus which may represent limbic encephalitis *vs*. postictal oedema. (C, D) demonstrate resolution of previous T2 hyperintense T2 signal seven months later.

A new refractory seizure state and MRI findings suggesting limbic encephalitis should serve as red flags for an autoimmune encephalitis, including anti-GABA(B) encephalitis. Our patient responded well to immunotherapy, similar to a treatment algorithm for autoimmune encephalopathies (Rosenfeld and Dalmau, 2011) and three months of a pharmacologically-induced coma. This case emphasizes that anti-GABA(B) encephalitis patients presenting with NORSE can have a good prognosis if recognized and treated early with aggressive multi-modal immune suppression. It also suggests that there may be a benefit for more widespread testing of CSF and serum for autoantibodies targeting the GABA receptor in patients who present with refractory seizures.

Table 1. Results of significant laboratory and radiological studies.

Laboratory Studies		
Sample	**Test**	**Results**
Serum	ANA (Anti-nuclear Antibodies)	(-)
	Nuclear Antibody Panel: anti-dsDNA, anti-Ribonucleoprotein, anti-Smith, anti-SS-A, anti-SS-B, anti-SCL-70, anti-Jo-1, anti-centromere, anti-Histone	(-)
	NMDA-receptor antibody	(-)
	Voltage-gated potassium channel antibody	(-)
	Voltage-gated calcium channel antibody	(-)
	Other paraneoplastic: anti-Hu, anti-CV2, anti-Yo, anti-Ri, anti-CAR, anti-Ma, anti-Ta, anti-Zic4, anti-R1, anti-LGI1, anti-CASPR2	(-)
	Microbiology: trypanosome cruzi, CMV, West Nile, Bartonella henselae, VZV, Lyme, HIV, Rabies, Coxiella	(-)
CSF	WBC	16 (L95%, M 5%)
	RBC	0
	Glucose	71 mg/dL (40-70 mg/ dL)
	Protein	24 mg/ dL (15-45 mg/ dL)
	Myelin Basic Protein	(-)
	NMDA-receptor antibody	(-)
	GABA(B) receptor antibody	(+)***
	14-3-3 (Berg *et al*., 2003)	(+), this viewed as a non-specific marker that can be seen in status epilepticus
	Microbiology: toxoplasmosis, VDRL, Cryptococcal, Lyme, HSV-1, HSV-2, West Nile Virus, CMV, VZV, EBV, Enteroviruses, Eastern equine encephalitis, La Crosse encephalitis, Saint Louis encephalitis, Western equine encephalitis, bacterial culture, AFB culture, AFB culture	(-)
Urine	Urinalysis	(-)
	Urine drug screen	(-)
	Chlamydia/Gonorrhea	(-)

Table 1. Results of significant laboratory and radiological studies. (*Continued*)

Radiological Testing	
Imaging Study	**Results**
CT Head without contrast	(-)
Brain MRI with/without gadolinium	(-) initially, subsequent development of T2 hyperintensity and enlargement of L-hippocampus, later resolved
Chest CT/Abdomen/Pelvis with/without contrast (*multiple studies, worst results reported*)	No evidence of malignancy
Testicular Ultrasound (*multiple studies, worst results reported*)	No evidence of malignancy
Whole-Body PET Scan (*multiple studies, worst results reported*)	Faint metabolic activity in otherwise unremarkable lymph nodes in the right cervical nodal chain subcarinal region, right hilum, and the left inguinal area. Most likely reactive

(-): negative or normal test result; (+): positive or abnormal.
***GABA(B) receptor antibody positivity was found after sending serum/CSF samples to the Institut d'investigacions biomédiques August Pi I Sunyer (IDIBAPS) in Barcelona, Spain. Anti-GAD(65), which is frequently reported in patients with positive GABA(B)-receptor antibodies, was not tested or at least not reported to the authors as having been tested.

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None of the authors have any conflicts of interest to declare.

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TEST YOURSELF

(1) Autoimmune encephalitides are known to be associated with antigens targeting which of the following structures?
A. NMDA-receptor
B. AMPA-receptor
C. GABA(B)-receptor
D. LGI1-protein
E. CASPR2-protein
F. All of the above

(2) Which cancer is most often associated with GABA(B) limbic encephalitis?
A. Ovarian teratoma
B. Breast cancer
C. Small cell lung cancer
D. Testicular cancer
E. Hodgkin's disease

(3) Which of the following is NOT a modality of immune-suppressive therapy?
A. IV methylprednisolone 1000 mg IV x 5 days
B. Intravenous immunoglobulins (IVIG) 0.4 g/kg/day x 5 days
C. IV cyclophosphamide 750 mg/mˆ2 once monthly
D. Therapeutic plasma exchange (PLEX) x 5-7 treatments
E. IV rituximab (375 mg/Mˆ2) weekly x 4 weeks
F. Tumour resection (if discovered)
G. IV midazolam 0.20 mg/kg bolus, then 0.05 to 0.60 mg/kg/hr continuous infusion

Note: Reading the manuscript provides an answer to all questions. You can check for the correct answer by visiting the Educational Centre section of www.epilepticdisorders.com