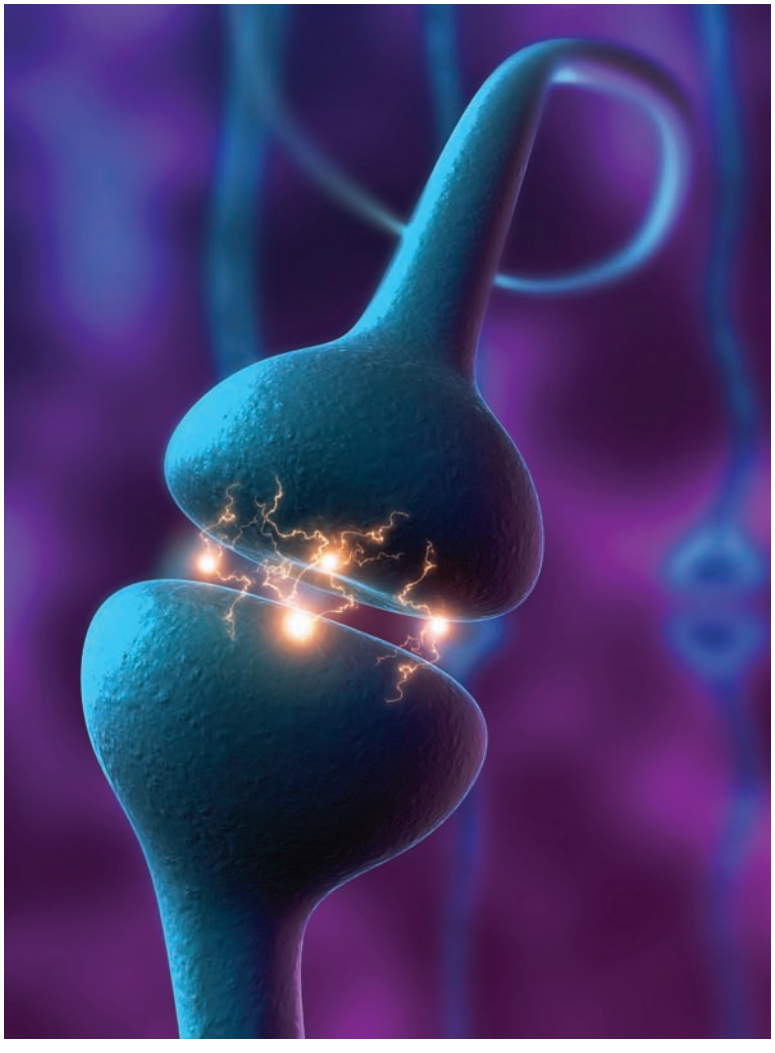
CASE REPORT

# A young man with altered mental status and new-onset seizures

Richard S. Cassa, MPAS, RPA-C; Axel J. Rosengart, MD, PhD, MPH



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## ABSTRACT

Signs and symptoms of a subacute, progressive, imaging-negative encephalopathy can be misdiagnosed as a neuropsychiatric or progressive neurodegenerative disorder. However, encephalopathies often can be reversed if the autoimmune component is recognized early through a careful history and diagnostic testing, including cerebrospinal fluid analysis for antibodies.


**Keywords:** seizures, acute delirium, *N*-methyl-D-aspartate receptors, autoimmune encephalopathy, neural-specific autoantibodies

## CASE

A 31-year-old right-handed man was referred for bizarre behavior and distractibility that over 4 weeks developed into frank delusions, personality changes with anxiety, disorganized speech, and a series of grand mal seizures. He did not seek medical attention until the day of admission, when his parents brought him to the ED. The patient had a history of treated, non-insulin dependent diabetes and hypertension; his family reported recent weight loss and persistent sleepiness in the weeks before hospital admission. The family denied any history of recent travel, headaches, or seizures. The patient's social history was positive for moderate tobacco use but was negative for illicit drug or alcohol consumption.

His vital signs were: heart rate, 106; respirations, 22; BP, 145/87 mm Hg; and $Spo_2$, 100% on room air. He was afebrile and awake. He opened his eyes with some random fixations but had no sustained interactions with the environment. He had intermittent perseverations of unintelligible phrases; persistent hyperkinetic smacking-like oropharyngeal movements, and dystonia of his upper extremities. He had normal motor, sensory, and cerebellar examinations except for brisk reflexes throughout. His general examination was unrevealing. Analysis of his cerebrospinal fluid (CSF) showed a normal opening pressure; 16% lymphocytes; 2,000 red blood cells/$mm^3$; protein of 37 mg/dL; and glucose of 142 mg/dL. His urine and blood toxicologies were negative. Blood and CSF cultures and viral panels were also negative. Results also were negative for acid-fast bacillus polymerase chain

**Richard S. Cassa** is a senior PA in the department of neurology, division of acute neurosciences at New York Presbyterian Hospital-Cornell in New York City. **Axel J. Rosengart** is director of neurocritical care and an associate professor of neurology, neuroscience, and neurosurgery at Weill Cornell Medical College in New York City. The authors have indicated no relationships to disclose relating to the content of this article.

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reaction, antinuclear antibody (ANA) testing, rheumatoid factor, antineutrophil cytoplasmic antibody testing, venereal disease research laboratory testing, and viral panels including HIV, Epstein-Barr, cytomegalovirus, herpes simplex, and West Nile. Antibodies to *N*-methyl-D-aspartate (NMDA) receptors, and anti-Hu and anti-Ma were positive. Other paraneoplastic antibody titers were negative.

Video-EEG identified left frontal anterior temporal lobe slowing with focal spikes; these spikes correlated with clinically visible focal motor discharges and secondary generalization to tonic-clonic seizures (**Figures 1-3**). Initial and repeated brain MRIs with gadolinium, magnetic resonance angiography, and magnetic resonance spectroscopy (with special attention to the bilateral frontal and temporal regions) were unrevealing as was a whole body positron emission tomography (PET) scan. Testicular ultrasound and contrast-enhanced CT of the chest, abdomen, and pelvis were inconspicuous.

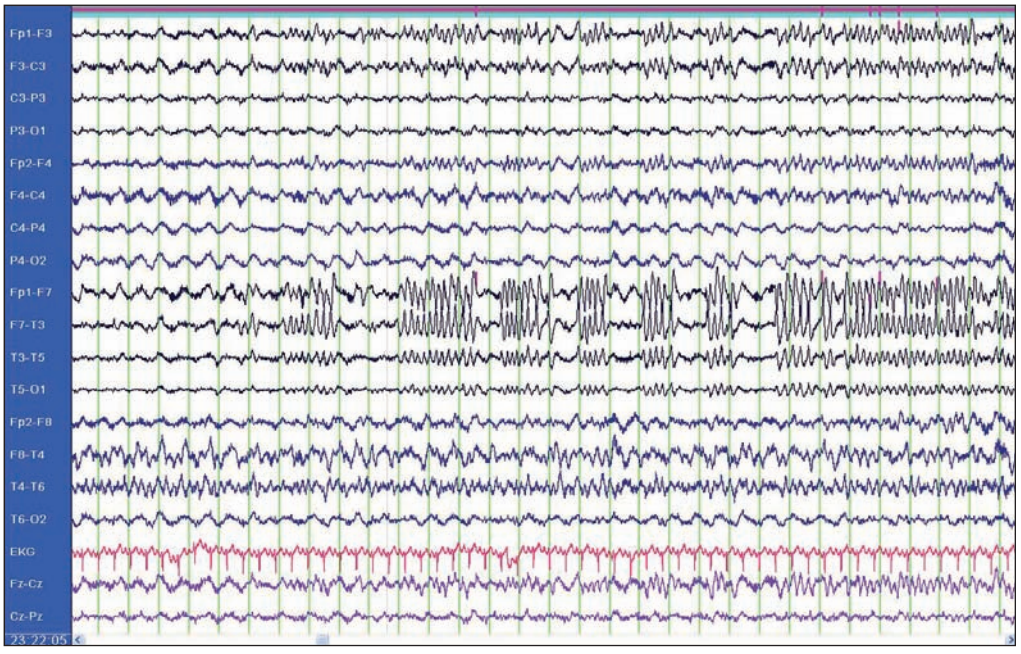



**FIGURE 1.** Video-EEG showing left frontal anterior temporal focal seizure with secondary generalization (channels Fp1-F3, F3-C3)

## DISCUSSION

In this patient, the history, clinical assessment and initial diagnostic findings illustrate the neuropsychiatric-neurologic presentation of a subacute, progressive, imaging-negative encephalopathy in a young man. The associated syndrome usually presents with psychiatric manifestations (less frequently with short-term memory deficits) and may evolve to life-threatening complications including seizures, hypoventilation, and autonomic instability.[1] Such rapidly progressive syndromes can be named autoimmune encephalopathies, such as in our patient, who had acute delirium. The syndromes also can be called autoimmune dementia if a progressive course leads to progressive cognitive decline without the presence of delirium. PAs must appreciate the potential for reversibility of such encephalopathies and the great risk of misdiagnosing patients with a neuropsychiatric or progressive neurodegenerative disorder. Such misdiagnoses can have devastating consequences to the patient, leading to irreversible neurologic damage or death.

Unfortunately, the current classification for these encephalopathies is confusing—the various approaches include using eponyms, syndromes, serological markers, or pathological findings, and may change even more as new, disease-inducing antibodies are identified. The authors recommend a serological classification such as anti-NMDA receptor encephalopathy whenever possible; otherwise, descriptive terms, such as progressive encephalopathy with rigidity and myoclonus, can be used to best describe the clinical syndrome in a patient.

Look for the diagnostic key points of cognitive decline and autoimmunity. First, the clinical manifestation of neuroimmunity is often multifocal and varies among different syndromes. Patients may present with acute neuropsychiatric syndromes and delirium or a slowly progressive dementing illness. On examination, determine if the patient has had an acute or subacute decline in memory, thinking, or behavior. For example, many neuro-autoimmune cognitive disorders present as limbic encephalitis with fluctuating confusional state, agitation, memory loss, hallucination, and focal or generalized seizures. Other patients, however, have an even more insidious onset, including impairment of learning new information and slowed processing associated with increasing abnormalities in language, behavior, reasoning, or manual tasks (praxis). Day-to-day fluctuations in the patient's neurologic status are commonly observed and spontaneous remission may occur. To monitor a patient's cognitive status, obtain repeated objective cognitive testing (for example, at the bedside or as neurocognitive evaluations).

Second, search for a personal or family history of autoimmunity or seropositivity for organ-specific and non-organ-specific autoantibodies as risk factors. Take a cancer history and ask patients about cancer risk factors,

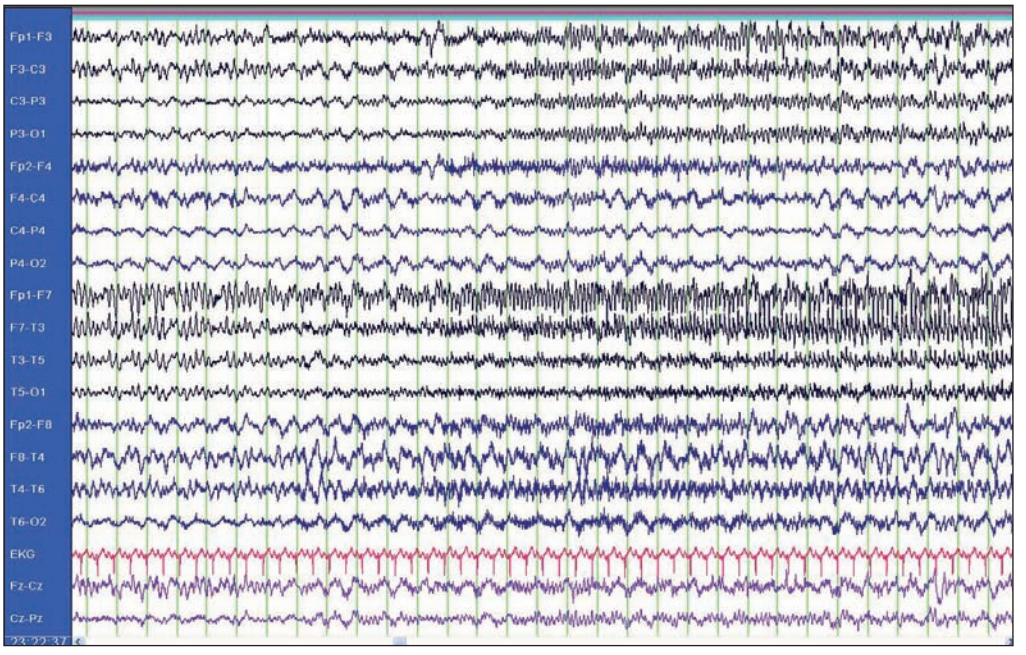



**FIGURE 2.** Evolution of seizures (channels Fp1-F3, P3-O1, Fp1-F7, T3-T5)

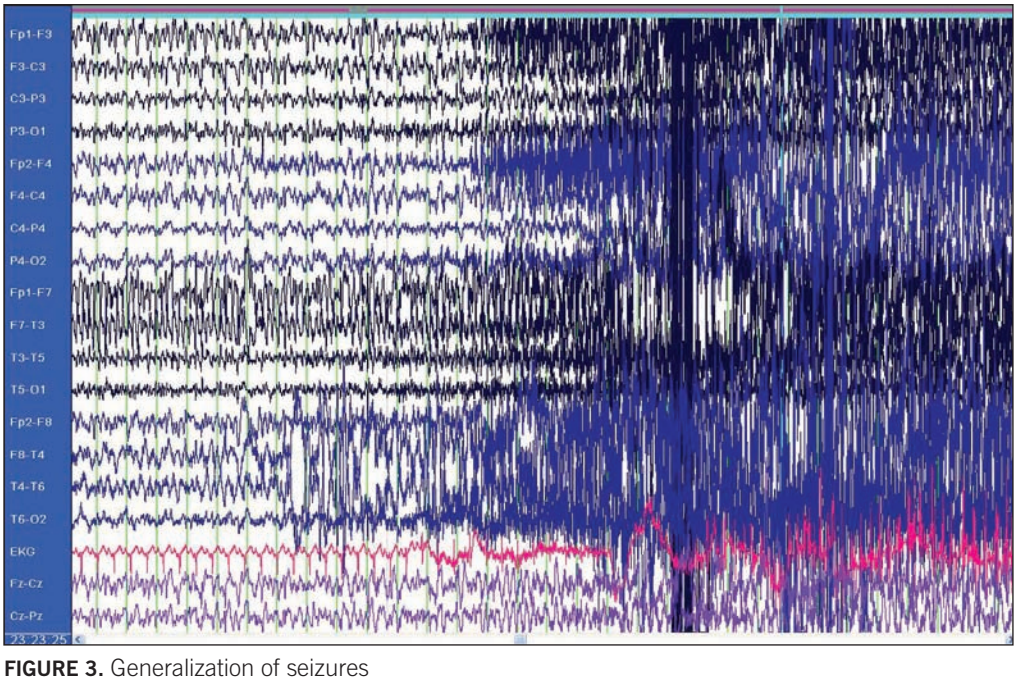
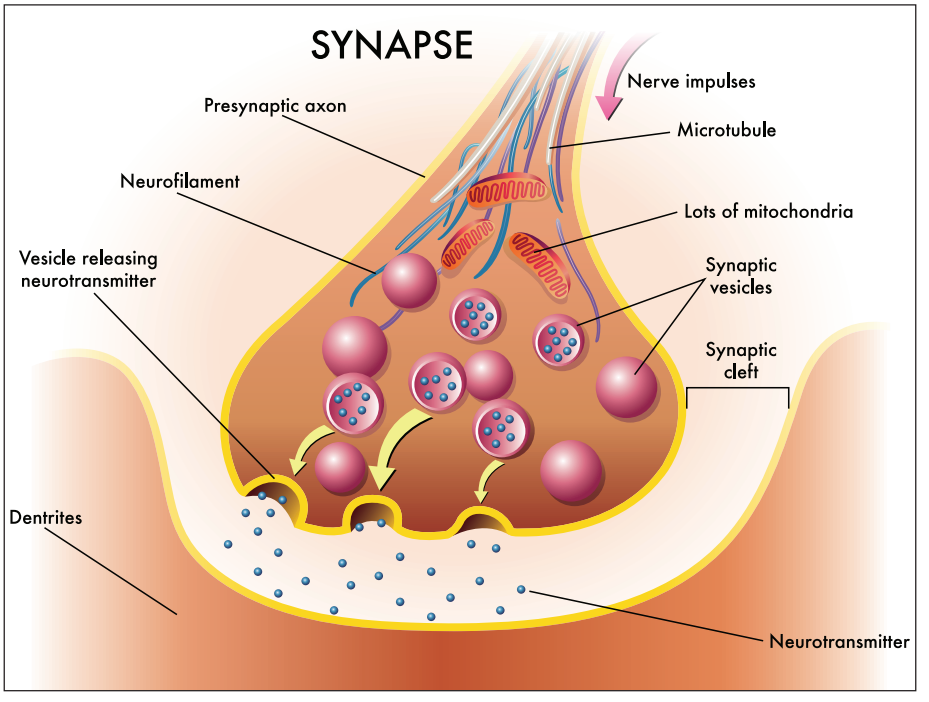



**FIGURE 3.** Generalization of seizures

smoking, and unexplained weight loss. Remember that patients with autoimmune diseases are at higher risk for developing a second autoimmune disorder (for example, thyroiditis and dementia).

Third, identify neural-specific autoantibodies as a marker for the disease.[2] Generally, these antibodies can be directed against cell surface antigens such as receptors or against an intracellular antigen such as nuclear antigens. Detection of autoantibodies in serum or CSF of non-neural autoantibodies does not make the diagnosis of autoimmune encephalopathy but strongly supports its consideration. Remember that different antibodies have different paraneoplastic causes, but the presence of a neuronal antibody does not imply that a cancer must be present. For example, the positive predictive values for cancer detection in a patient harboring neural autoantibodies varies from 33% in voltage-gated potassium channel antibodies (associated with various cancers) to more than 80% in a patient with antineuronal nuclear antibody type 1 (ANNA-1) for hiding a cancer such as small-cell lung carcinoma.[3,4] Serum antibody testing usually is sufficient, but CSF testing may be required to increase the diagnostic yield, for example in the case of NMDA receptor antibodies. Most clinicians recommended simultaneous testing of serum and CSF. Other CSF parameters consistent with autoimmune encephalopathy include mild pleocytosis, protein greater than 100 mg/dL, oligoclonal bands, and elevated IgG index.

Lastly, a trial of immunotherapy leading to objective improvement on neuropsychiatric testing, seizure control, and imaging can serve as a valuable "diagnostic" test and is of therapeutic importance. A trial of high-dose IV prednisolone is often justified, but alternate-week IV immunoglobulin (IVIG) can be used in patients who cannot tolerate corticosteroids. Plasma exchange has been useful for more critically ill patients or when corticosteroids or IVIG are poorly tolerated. A treatment trial of 4 to 8 weeks is generally recommended and should be followed by objective testing for disease activity. Patients on corticosteroids often




report that they feel better. Many patients responding to initial therapy need to be maintained on chronic therapy to achieve meaningful cognitive and functional gains. To reduce the need for corticosteroids or to more aggressively reduce autoantibody burden, other disease-modifying agents such as azathioprine, cyclophosphamide, and methotrexate can be used. If the patient has an underlying tumor, resection is important to attain final recovery or sustain the improvement that in some cases starts soon after immunotherapy.[5]

In our patient, causes such as viral or bacterial infections were excluded by repeated CSF sampling. No structural or vascular abnormalities such as a tumor or vasculitis were found on brain imaging. Therefore, autoimmune encephalopathy seemed the most likely presumptive diagnosis. The patient was immediately started on high-dose corticosteroids after CSF and serum samples were collected for further testing. Ultimately, the patient was diagnosed with anti-NMDA receptor encephalitis. This severe form of autoimmune encephalitis, which mostly affects young people, is associated with antibodies against NR1-NR2 heteromers and results in a characteristic neuropsychiatric syndrome.[5] According to Dalmau and colleagues, 41% of patients with anti-NMDA receptor encephalitis do not have a clinically detectable tumor.[6] Because of the severity of this patient's illness and his initial poor response to IV corticosteroid therapy, he underwent plasmapheresis and received IVIG and the immunomodulator rituximab. His elevated BP was controlled with amlodipine, lisinopril, and metoprolol. His course was further complicated by bilateral pulmonary emboli; left lung pneumothorax during positive-pressure ventilation, which required a pigtail catheter for pleural drainage; and vancomycin-resistant *Enterococcus* pneumonia requiring pleurectomy and decortication of the left lower lobe. A testicular ultrasound and a whole body (including brain) PET scan were negative for tumor.

Over time, the patient's neurologic status improved and he was discharged from the ICU. At his time of discharge to rehabilitation three months later, he was awake, alert, and oriented x3, without psychiatric symptoms or seizures. He had a normal cranial nerve examination and had 4/5 extremity strength. Long-term follow-up one year later identified a completely recovered patient undergoing regular (and so far negative) cancer screening, who no longer required immunosuppressive therapy. **JAAPA**

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