

# Precipitously and certainly psychotic— but what's the cause?

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## How would you handle this case?

Answer the **challenge questions** throughout this article

Ms. L, age 38, rapidly becomes confused and agitated, and expresses suicidal ideation. Her history is not consistent with a typical course of mental illness. How would you treat her?

### **CASE** Sudden personality change

Ms. L, age 38, is brought to the university hospital's emergency department (ED) under police escort after she awoke in the middle of the night screaming, "I found it out! I'm a lie! Life is a lie!" and began threatening suicide. This prompted her spouse to call emergency services because of concerns about her safety.

Over the preceding 9 days—and, most precipitously, over the last 24 hours—Ms. L has experienced a dramatic "change in her personality," according to her spouse. In the ED, she is oriented to person, place, and time. Her vital signs are within normal limits, other than a mild tachycardia. Complete blood count and complete metabolic profile are unremarkable and a urine drug screen is positive only for benzodiazepines (she recently was prescribed alprazolam). Ms. L smiles inappropriately at the ED physicians and confides that she is hearing music by *The Lumineers*, despite silence in her room.

The psychiatry service is consulted after she is seen making threats of harm to her family members.

### **EVALUATION** Confusion

Over past several weeks, Ms. L has experienced rapid onset of neurovegetative symptoms, with poor oral intake, increased somnolence, neglect of hygiene, excessive

time spent in bed, and weight loss of 15 to 20 lb, according to her spouse. She also has been complaining of foggy mentation, weakening handgrip, and tinnitus. She has no previous psychiatric history.

She recently established care with an outpatient neurologist and infectious disease specialist to address these symptoms. Outpatient EEG and sexually transmitted infection (STI) tests were scheduled but not yet obtained. Ms. L's spouse observes that her drastic "personality change" over the preceding 24 hours coincided with her feeling upset and offended by a physician's recommendation to obtain STI tests (it is unclear why the physician recommended these tests).

Ms. L had presented to another local ED 4 times over several weeks for various complaints, and had been prescribed alprazolam, 0.5 mg, 3 times a day as needed, and buspirone, 15 mg/d, for anxiety. She also had received a short course of doxycycline, 200 mg/d, which she did not finish, for treatment of presumed Lyme disease. According to her spouse, Ms. L had completed a course

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of doxycycline for Lyme disease 1 year earlier, but the medical records are not available for review.

During the interview, Ms. L is fairly well groomed but appears confused; she asks her spouse if she is “real” and states that she feels “crazy.” She seems uncomfortable and is guarded, with a minimally reactive, anxious affect. She has general psychomotor slowing and her speech is soft and monotonous, with prominent latency. She reports passive suicidal ideations as well as active auditory hallucinations of a musical quality.

The Mini-Mental State Examination (MMSE) score is 19/30, indicating moderate cognitive impairment, and she is unable to complete attention, executive function, 3-stage command, and delayed word recall tasks. She reports fatigue, diarrhea, and decreased appetite. Her physical examination is notable for an overweight white woman without focal neurologic deficits. Her family psychiatric history reveals bipolar disorder in 2 distant relatives.

In the ED, Ms. L is given 3 provisional diagnoses:

- adjustment disorder, because of her reaction to the proposed STI testing
- psychotic disorder not otherwise specified, because of her obvious psychosis of unknown cause
- rule out delirium due to a general medical condition, because of her sudden onset of attention, perception, and memory difficulties.

As Ms. L sits in her room, her abnormal behaviors become more apparent. She starts to endorse active suicidal ideations and becomes aggressive, trying to choke her spouse, shouting, jumping on her bed, and attempting to strike herself. For her safety, she is physically restrained and given IM haloperidol, 10 mg, and IM lorazepam, 2 mg.

#### What would you do next to treat Ms. L?

- a) Admit her to the psychiatric unit for monitoring and treatment of psychosis and consider additional antipsychotics for agitation

- b) Perform a bedside lumbar puncture to assess for findings suggestive of a CNS infection or anomaly
- c) Sedate her with IM ketamine, intubate her, and admit her to the intensive care unit (ICU) for further medical workup
- d) Begin IV antibiotic therapy with ceftriaxone for early-disseminated Lyme disease with CNS involvement

#### The authors' observations

Clearly, Ms. L was psychotic. However, psychosis is a nonspecific term used to describe a heterogeneous group of phenomena in which one experiences an impaired sense of reality. Although commonly caused by psychiatric disorders, psychosis can arise from a variety of causes.<sup>1</sup> Ms. L's initial physical examination and laboratory studies were within the normal range, but her mental status exam and MMSE were abnormal. At this point, selecting the appropriate setting for further observation, workup, and treatment became important.

#### TREATMENT The right setting

Given the abrupt onset of Ms. L's symptoms, the treatment team is concerned about active neurologic or infectious disease. However, no acute laboratory or physical examination findings support this hypothesis, and the ED physicians conclude that no further emergent workup is indicated. Because Ms. L is threatening harm to herself and others, she cannot be safely discharged. The treatment team decides the safest option is to admit Ms. L to the inpatient psychiatric unit for observation, further non-emergent workup, and consultation with the neurology service.

**At admission.** Ms. L is cooperative and calm, lying in bed comfortably. She obeys simple commands; a brief neurologic examination is remarkable for a sedated female without focal motor or sensory deficits. Although her answers to questions are brief, they are

#### Clinical Point

**Although commonly caused by psychiatric disorders, psychosis can arise from a variety of causes**

### Clinical Point

Given her abrupt onset of symptoms, including auditory hallucinations, the team expresses concern for herpes simplex encephalitis

appropriate. She sleeps without incident for approximately 10 hours.

**The next morning.** Ms. L does not awaken to verbal or gentle physical stimuli. Upon sternal rub, she awakens and forcefully squeezes the examiner's arm, after which she closes her eyes and does not answer further questions (but does resist passive eye opening). After several minutes, she begins exhibiting verbigeration, shouting repeated phrases such as "The birds are in my ears" and "No, I am not okay."

An emergent EEG is ordered because the team is concerned about nonconvulsive status epilepticus and the neurology service is consulted about the need for an urgent lumbar puncture. Without any obvious abnormal physical examination findings, however, the neurology team's initial assessment attributes Ms. L's presentation to a primary psychiatric illness and does not recommend a lumbar puncture or EEG.

That day and night, Ms. L has several episodes of agitation with a disorganized thought process and perseverative speech. She appears distraught and exhibits menacing behaviors. She is poorly redirectable and physically hostile toward staff, requiring several emergent doses of IM haloperidol and IM lorazepam, to which she responds minimally. Ms. L is placed on constant observation, requiring frequent redirection from the rooms of other patients and intermittent seclusion because of her violent, destructive behavior.

**The next day.** Ms. L remains grossly agitated and psychotic. Although an EEG is ordered, it is not performed because the technicians are concerned about their safety. With her unclear history of Lyme disease and concern for an infectious encephalopathy, Ms. L's history and symptoms are discussed with the infectious disease service. Given her abrupt onset of symptoms, including auditory hallucinations, they express concern for herpes simplex encephalitis and recommend emergent treatment with IV acyclovir and ceftriaxone.

This recommendation, however, causes a practical conundrum. Because of state laws and differences in staff training, the treatment team believes that the inpatient psychiatric unit is not the appropriate setting to administer these IV treatments. At the same time, hospital security, nursing staff, and the receiving medical team are concerned about transporting Ms. L to the general medical floor.

**In the ICU.** After discussion, the teams decide that the safest and least traumatic option is to transport Ms. L to the ICU after she is sedated and intubated. In the ICU, she undergoes empirical treatment for herpes simplex encephalitis and further medical workup.

An EEG reveals findings suggestive of severe encephalopathy. A lumbar puncture shows lymphocytic pleocytosis with an opening pressure of 28 cm H<sub>2</sub>O and normal protein and glucose levels. Her serum C-reactive protein is slightly elevated at 1.4 mg/dL. She also is found to have an elevated herpes simplex virus (HSV)-2 IgG antibody.

**Subsequent hospital stay.** Ms. L has 2 episodes of seizure-like activity, for which she is treated with levetiracetam, 2,000 mg/d, increased to 3,000 mg/d. She is sedated for several days to allow broad treatment with antiviral and antibiotic medications. Although she experiences intermittent fevers and tachycardia, cultures of blood, urine, and cerebrospinal fluid (CSF) show no growth. Similarly, a test of serum HSV IgM antibodies is negative.

CT of the chest, abdomen, and pelvis reveals no findings suggestive of malignancy but does show a solid-appearing 6-mm nodule in her right lung. Magnetic resonance angiography of the head and neck shows no evidence of abnormalities other than atrophy of the superior cerebellar vermis and a subtle focus of T2/FLAIR signal abnormality in the medial portion of the left occipital lobe.

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**Table 1****Phases of anti-NMDA receptor encephalitis**

Phase	Common time frame	Signs and symptoms
Viral-like prodrome	As long as 2 weeks before other manifestations	<ul style="list-style-type: none"> <li>• <b>Lethargy</b></li> <li>• <b>Headache</b></li> <li>• Upper respiratory symptoms</li> <li>• Nausea</li> <li>• Diarrhea</li> <li>• <b>Myalgias</b></li> <li>• Fever</li> </ul>
Psychiatric manifestations	1 to 3 weeks after initial onset of symptoms	<ul style="list-style-type: none"> <li>• <b>Delusional thought content</b></li> <li>• <b>Disorganized thoughts and behaviors</b></li> <li>• <b>Agitation</b></li> <li>• <b>Perceptual disturbances</b></li> <li>• <b>Anxiety and fear</b></li> <li>• <b>Bizarre behaviors, behavioral outbursts</b></li> <li>• <b>Personality changes (can be the initial symptom)</b></li> <li>• <b>Mood lability</b></li> <li>• <b>Echolalia, mutism, or both</b></li> <li>• Paranoia</li> <li>• Sleep dysfunction</li> <li>• Hypersexuality</li> <li>• <b>Blunted affect</b></li> </ul>
Severe neurologic manifestations	2 weeks to 4 months after initial onset of symptoms	<ul style="list-style-type: none"> <li>• <b>Global alteration of consciousness</b></li> <li>• Catatonia</li> <li>• Abnormal movements (orofacial dyskinesias, dystonic posturing, choreiform movements)</li> <li>• <b>Autonomic instability</b> (hyperthermia, tachycardia or bradycardia, hypotension or hypertension)</li> <li>• Hypoventilation</li> <li>• <b>Complex or partial motor seizures</b></li> </ul>

Note: Bolded items were part of Ms. L's presentation

NMDA: *N*-methyl-D-aspartate

Source: References 2,3

**Clinical Point**

Without any obvious abnormal physical exam findings, neurology attributes Ms. L's presentation to a primary psychiatric illness

**The following weeks.** Ms. L's cognitive status improves markedly. Extensive studies—including serum ammonia, thyroid-stimulating hormone, Lyme disease antibody, vitamin B<sub>12</sub>, folate, beta-hCG, HIV, hepatitis B and C, *Varicella zoster*, syphilis, Lyme disease serology, CSF Eastern equine encephalitis, St. Louis encephalitis virus, West Nile virus, *Ehrlichia chaffeensis*, *Babesia microti*, Rocky Mountain spotted fever, John Cunningham virus, typhus fever, cryptococcal antigen, rabies, 2 serum tests for anti-*N*-methyl-D-

aspartate (NMDA) receptor antibodies, and serum ceruloplasmin—are normal.

At discharge, Ms. L's clinical presentation is thought to be most consistent with viral encephalitis, because of her CSF lymphocytic pleocytosis, fever, and improvement with supportive care. Because she improves, the team does not find it necessary to wait for results of pending studies, including a paraneoplastic autoantibody panel and a CSF anti-NMDA receptor antibody, before discharging her.

**Readmission.** Although the results of the paraneoplastic autoantibody panel are unremarkable, several weeks after discharge Ms. L's CSF anti-NMDA receptor antibodies return positive, despite 2 earlier negative serum studies. She is readmitted to the neurology service for treatment with immunomodulators.

A positron-emission tomography scan is negative for malignancy. She is treated on an ongoing basis with immunomodulators; cognition improves such that she is able to start working again with good overall functioning. Despite this improvement, she experiences residual sequelae, including noise sensitivity, amnesia of the events surrounding her hospitalization, mild short-term memory deficits, and persistent affective blunting.

### The authors' observations

Psychosis is not exclusive to psychiatric syndromes and frequently is a symptom of an underlying neurologic, immunologic, metabolic, infectious, or oncologic abnormality.<sup>1</sup> Anti-NMDA receptor encephalitis is an autoimmune disease in which antibodies attack NMDA-type glutamate receptors at central neuronal synapses and can produce psychosis, as seen with Ms. L<sup>2</sup> (*Table 1, page 62*<sup>2,3</sup>). The etiology of the disease is not fully understood. Determining the appropriate setting to perform a complete medical workup in a severely agitated patient after an initial negative medical workup can be challenging.

### What's the most appropriate treatment setting?

This case illustrates the importance, with any new-onset psychosis, of weighing heavily a carefully obtained psychiatric history, even in the absence of focal physical examination and initial laboratory abnormalities. It also highlights the challenge of determining the most appropriate initial setting for performing the important task

**Table 2**

### Common entities in the differential diagnosis of anti-NMDA receptor encephalitis

Bipolar disorder
Dissociative disorder
Klüver-Bucy or Kleine-Levin syndromes
Malingering
Nonconvulsive status epilepticus
Neuroleptic malignant syndrome
Schizoaffective disorder
Schizophrenia
Substance-induced psychosis
Viral encephalitis
NMDA: <i>N</i> -methyl-D-aspartate
Source: References 1,2

of a complete medical workup for first-episode psychosis.

Ms. L initially was treated in the inpatient psychiatric unit because of safety concerns and practical limitations, but was later found to have a disease that could not be managed in that setting. She proved to be too agitated to obtain a full medical workup on the inpatient psychiatric or general medical floors and required transfer to the ICU. Despite her normal basic laboratory tests, her EEG and CSF studies did demonstrate abnormalities, suggesting these can be useful to the basic workup for psychosis of unknown cause (*Table 2*<sup>1,2</sup>).

This case also demonstrates that negative serum anti-NMDA receptor antibody tests do not rule out the disease; one study found that only 85% of patients with CSF anti-NMDA receptor antibodies also had detectable antibodies in their serum and that detectability changed during the course of the disease.<sup>4</sup> This supports the utility of a lumbar puncture as part of a basic initial workup for some cases of new-onset psychosis. Because clinical outcomes often correlate with early treatment, as with anti-NMDA receptor

### Clinical Point

**This case also demonstrates that negative serum anti-NMDA receptor antibody tests do not rule out the disease**

**Clinical Point**

**Anti-NMDA receptor encephalitis is an autoimmune disease in which antibodies attack NMDA-type glutamate receptors**

**Table 3**  
**Recommended workup of patients with suspected anti-NMDA receptor encephalitis**

Complete blood count, comprehensive metabolic panel, urine drug screen, reflexive TSH
EEG (usually abnormal, showing slow and disorganized activity <sup>5</sup> )
Serum and CSF NMDA receptor antibodies
Lumbar puncture (common findings include moderate lymphocytic pleocytosis, elevated protein, and oligoclonal bands <sup>6</sup> )
Neurologic examination
Pelvic imaging to evaluate for ovarian teratoma (in females)
Psychiatric history
Vital signs
CSF: cerebrospinal fluid; NMDA: N-methyl-D-aspartate; TSH: thyroid-stimulating hormone

encephalitis, a timely diagnostic workup of psychosis often can be important.<sup>3,5</sup> The ICU can be considered an appropriate setting for working up some patients who develop new, rapid-onset psychosis and severe agitation, even in the absence of initial laboratory or physical examination findings.

Ms. L's case also illustrates the importance of completing a thorough medical workup for patients with new-onset psychosis before transferring them to an independent psychiatric hospital. Initially, the university's psychiatric unit was at capacity and a bed was sought at outside psychiatric hospitals while Ms. L waited in the

ED. Had Ms. L not been admitted to a large academic medical center, she may not have had access to the multidisciplinary collaboration that proved necessary for the appropriate diagnosis and treatment of her anti-NMDA receptor encephalitis (*Table 3*<sup>5,6</sup>).

**What prodromal symptoms occur as long as 2 weeks as an initial presentation in many patients with anti-NMDA receptor encephalitis?**

- a) Flu-like symptoms of lethargy, headache, gastrointestinal symptoms, myalgias, fevers, and upper respiratory symptoms
- b) Delusions, hallucinations, disorganized behaviors and thoughts, behavioral outbursts, hypersexuality, mood lability, personality change, paranoia, echolalia, mutism, anxiety, agitation, aggression, hyperactivity, sleep dysfunction, and blunted affect
- c) Dyskinesias, autonomic instability, central hypoventilation, and seizures

**NEXT MONTH IN CASES THAT TEST YOUR SKILLS**

Mr. X, age 67, develops cognitive impairment, gait disturbance, dyskinesia, and urinary incontinence over 2 months. Imaging reveals enlarged ventricles and some cortical atrophy. For 8 years he has been taking valproic acid and venlafaxine for bipolar depression. What is your diagnosis?

Follow this case in the June 2016 issue of



**The authors' observations**

Lab results, vital signs, and physical examination should not supplant a careful history when determining an appropriate clinical course of action. As experts in the cognitive sciences, psychiatrists may be

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the most qualified in determining whether a patient with new-onset psychosis should undergo further medical testing before a condition is deemed to be solely of a psychiatric cause. As a neurologic disease of immunologic origin with psychiatric manifestations, anti-NMDA receptor encephalitis is a complex condition requiring collaboration among several specialists for appropriate management.

#### References

1. Freudenreich O. Differential diagnosis of psychotic symptoms: medical “mimics.” *Psychiatric Times*. <http://www.psychiatrytimes.com/forensic-psychiatry/differential-diagnosis-psychotic-symptoms-medical-mimics>. Published December 3, 2012. Accessed March 31, 2016.
2. Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis in psychiatry. *Curr Psychiatry Rev*. 2011;7(3):189-193.
3. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10(1):63-74.
4. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol*. 2014;13(2):167-177.

#### Related Resources

- The Anti-NMDA Receptor Encephalitis Foundation Inc. What is anti-NMDA receptor encephalitis? [www.antinmdafoundation.org/the-illness/what-is-anti-nmda-receptor-encephalitis](http://www.antinmdafoundation.org/the-illness/what-is-anti-nmda-receptor-encephalitis).
- Kruse JL, Jeffrey JK, Davis MC, et al. Anti-N-methyl-D-aspartate receptor encephalitis: a targeted review of clinical presentation, diagnosis, and approaches to psychopharmacologic management. *Ann Clin Psychiatry*. 2014;26(2):111-119.

#### Drug Brand Names

Acyclovir • Zovirax	Haloperidol • Haldol
Alprazolam • Xanax	Ketamine • Ketalar
Bupirone • Buspar	Levetiracetam • Keppra
Ceftriaxone • Rocephin	Lorazepam • Ativan
Doxycycline • Vibramycin	

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5. Dalmau J, Gleichman AJ, Hughes EC, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091-1098.
6. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61(1):25-36.

#### Clinical Point

Lab results, vital signs, and physical exam should not supplant a careful history when determining an appropriate clinical course of action

## Bottom Line

Psychosis is a symptom of various pathologies, not only psychiatric disorders, and could indicate a disease process that requires treatment by other specialists. Normal basic lab results, vital signs, and physical examination should not supersede a careful history when considering a further medical workup. Anti-N-methyl-D-aspartate receptor encephalitis can cause psychosis and should be considered in the evaluation of patients who present with an atypical psychotic prodrome.