Altered Mental Status

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ABSTRACT

Purpose of Review: Altered mental status is a common reason for neurologic consultation. Although it is often due to a systemic infection or metabolic derangement, a host of other etiologies can lead to irreversible brain injury if they are not promptly identified and treated. A systematic approach to the patient is important, with an understanding of when to initiate a more advanced and potentially more resource-intense diagnostic workup.

Recent Findings: The last decade has seen advances in both the diagnosis and treatment of altered mental status. A significant step forward in the diagnosis of patients with otherwise unexplained encephalitis has been the identification of numerous antibodies associated with paraneoplastic and nonparaneoplastic autoimmune encephalitis. The use of continuous electroencephalography has shown that a significant proportion of otherwise unexplained altered mental status may be caused by nonconvulsive seizures. Several studies have demonstrated that proactive, multi-component interventions may be effective in preventing hospital-acquired delirium. The recent introduction of dexmedetomidine may lead to decreased rates of delirium in the intensive care unit if the results of clinical trials are borne out in practice.

Summary: This article discusses causes of altered mental status, an initial approach to evaluating the patient, and elements of the advanced diagnostic workup. The article concludes with a general discussion of prevention and treatment.

INTRODUCTION

Altered mental status is broadly defined as a change in cognitive function or level of consciousness. It is a common reason for emergency department visits, hospitalization, and neurology consultation. As many as 5% to 10% of emergency department patients have altered mental status, with significantly higher rates among the elderly; over half of these patients are admitted to the hospital.\(^1\),\(^2\) Mortality rates for these patients are high, approaching 10% in some studies.\(^2\) Studies of delirium, which represents a large subset of patients with altered mental status, consistently report a prevalence of 10% to 31% among elderly patients who are hospitalized, with rates approaching 80% in the intensive care unit.\(^3\),\(^4\) At our hospital, approximately 15% of neurology consult requests are for altered mental status.

The differential diagnosis for altered mental status is broad and includes life-threatening yet treatable conditions; therefore, a systematic approach to the patient is necessary. Most internal medicine hospitalists and emergency department physicians are comfortable performing the initial workup, and neurologists are usually consulted only when a focal lesion is suspected or no immediate cause can be found. This article briefly discusses the initial approach to the patient with altered mental status and then delves into a more detailed discussion of the advanced workup and less common diagnoses with which the neurologist should be familiar.
DEFINITIONS AND LOCALIZATION

In their landmark monograph, Posner and Plum describe consciousness as having two components: content and arousal. The content of consciousness refers to the higher-level cortical processing that allows for awareness of self and environment and enables interaction with that environment. In the current conception of brain function, these processes are understood to be carried out by cortical regions and more widespread neuronal networks. For example, the ability to recognize both written and oral language, interpret its meaning, and produce speech is a part of consciousness usually served by regions in the left temporal and frontal lobes and their connections. A focal lesion in one of these regions may lead to a change in the content of consciousness but will not affect arousal.

Arousal refers to the level of alertness. Pathologic states of arousal range from coma, a state of complete unresponsiveness without eye opening, to drowsiness, in which a patient is arousable but needs stimulation to stay awake, to hypervigilance, where patients are awake but unable to focus their attention and are easily distracted by extraneous stimuli. If such patients are able to communicate, they almost universally have a deficit of attention and appear disoriented and confused. Arousal is maintained by various systems of neurons, most of which are located in the brainstem, hypothalamus, basal forebrain, and thalamus and project diffusely throughout the cortex. A lesion interrupting these projections in the brainstem, bilateral thalami, or diffusely in both hemispheres can lead to changes in level of arousal.

Altered mental status results from a change in either the content of consciousness or the level of arousal.

Thiamine administration should be considered in all patients with altered mental status because it is benign and Wernicke encephalopathy is reversible if treated promptly.

Encephalopathy is also a nonspecific term, often used interchangeably with altered mental status, which implies a diffuse process causing a change in the level of arousal. The term will be used in this manner throughout this article. Delirium is a more specific term, defined as an acute change in mental status characterized by a deficit in attention and a fluctuating course with either disorganized thinking or change in the level of arousal. Most changes in the content of consciousness, such as aphasia or neglect, are readily discernible upon examination, and such patients are usually easily triaged. Occasionally, however, a focal deficit may be misclassified as delirium by an inexperienced clinician; conversely, delirium may rarely be caused by a focal lesion. In addition, some processes may cause both focal deficits and delirium. Examples are basilar meningitis or a large hematoma with mass effect leading to hemiparesis and decreased responsiveness. The neurologist’s task is to take a careful history and perform a detailed physical examination in order to make these distinctions and direct an appropriate workup.

INITIAL APPROACH TO THE PATIENT

The first step in the evaluation of a patient with altered mental status is to establish the time course. Acute altered mental status is a medical emergency. A patent airway and intact circulation must be ensured, followed by measurement of vital signs and serum glucose. A focused neurologic examination is imperative to rule out structural lesions, such as a large stroke or hemorrhage, requiring emergent management. Naloxone should be administered if narcotic overdose is suspected; thiamine and glucose are also given routinely. Thiamine should always be administered with or before glucose to avoid precipitation of...
Wernicke encephalopathy. Once the patient is stabilized, further data gathering can be initiated (Table 1-1).

After the time course is established, the history should focus on determination of baseline cognitive function and whether any previous episodes of altered mental status have occurred. Other important elements of the history include symptoms of infection such as fever, headache, stiff neck, cough, or dysuria; current medications and recent medication changes; recreational drug and alcohol use; and history of recent trauma. Specific attention should be paid to medications known to cause delirium, such as those with anticholinergic properties, benzodiazepines, and narcotics.

### TABLE 1-1 Basic Approach to Altered Mental Status

- **Step 1 (All Patients)**
  - Airway, breathing, and circulation; vital signs; blood glucose level
  - If glucose is low, administer thiamine and dextrose; consider naloxone in the event of a possible opiate overdose

- **Step 2 (All Patients)**
  - History (special attention to baseline cognitive status, medications, symptoms of infection)
  - Physical examination (special attention to signs of infection; careful neurologic examination to rule out a focal deficit)
  - Complete blood count, electrolyte panel including calcium, magnesium, and phosphorus
  - Liver and kidney function tests, including albumin
  - Urinalysis and culture, urine toxicology screen
  - **Chest radiograph**
  - **ECG**

- **Step 3 (Guided by Findings on the Initial Evaluation)**
  - Brain imaging with CT followed by MRI with diffusion and gadolinium if the cause remains unclear
  - **Lumbar puncture (perform immediately after CT if meningitis is suspected; probably underused in patients presenting to medical care with altered mental status; usually not necessary for hospital-acquired encephalopathy unless the patient is immunocompromised or neurosurgical)**

- **Step 4 (Guided by Findings on the Initial Evaluation)**
  - Serum ammonia, thyroid function tests, morning cortisol, vitamin B₁₂, arterial blood gas
  - Sedimentation rate, autoimmune serologies including antinuclear antibodies, thyroperoxidase, and thyroglobulin antibodies
  - Blood cultures
  - Extended toxicology screen
  - EEG (perform sooner if high suspicion for status epilepticus)
KEY POINTS

- The history should focus on the time course, baseline cognitive function, medication use (including over-the-counter drugs and herbs), alcohol and drug abuse, symptoms of infection, and recent trauma.

- A careful neurologic examination is required in patients with altered mental status to rule out a focal deficit, the presence of which should prompt urgent neuroimaging.

- The most significant risk factors for delirium are advanced age and preexisting cognitive dysfunction.

A history of comorbid conditions that could contribute to altered mental status (such as cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, epilepsy, psychiatric disease, or immune compromise [including HIV infection]) should be sought.

The general physical examination should focus on potential medical causes of altered mental status. The head should be examined for signs of trauma. Percussion and auscultation of the lungs may reveal evidence of pneumonia or chronic obstructive pulmonary disease. Examination of the heart and extremities may show signs of endocarditis or congestive heart failure. Inspection of the skin can demonstrate signs of liver disease or needle marks indicating injection drug abuse. The presence of asterixis may point toward metabolic encephalopathy. Signs of meningitis should be sought, including meningismus and the peta-chial rash associated with meningococccmia. However, the decision regarding whether to pursue a lumbar puncture should never rest solely on the presence or absence of meningismus, because several studies suggest nuchal rigidity, Kernig sign, and Brudzinski sign are insensitive. Even jolt accentuation of headache (worsening of headache upon passive head turning at 2 to 3 rotations per second), touted as having a high sensitivity for meningitis in its original description, was found to be very insensitive in a subsequent study.

More critical for the neurologist is a careful search for a focal deficit. Patients with psychosis are usually oriented and have normal attention despite the presence of delusions, hallucinations, and disorganized thinking. Several stroke subtypes can present with changes in mental status ranging from abulia (in thalamic or orbital frontal infarcts) to agitation (in posterior cerebral artery infarcts and nondominant parietal lobe infarcts) to Wernicke aphasia (which can be initially mistaken for psychosis or delirium in left middle cerebral artery infarcts) to coma (with basilar artery occlusion). The focal signs that usually accompany such lesions may be overlooked by the non-neurologist. Focal deficits accompanying altered mental status may also be seen in lesions causing mass effect or hydrocephalus or in those associated with meningitis. In cases where a focal deficit is found, brain imaging is mandatory. If a large vessel occlusion is suspected, vascular imaging with CT or magnetic resonance angiography should also be performed.

The final part of the initial evaluation involves laboratory testing to rule out metabolic derangements and common infections that lead to altered mental status. This includes a complete blood count; measurement of electrolytes including calcium, magnesium, and phosphorous; and tests of renal and liver function. Urine should be analyzed for infection and drugs of abuse. An arterial blood gas may be helpful in revealing hypoxia or hypercarbia; a potential clue to the latter is an elevated bicarbonate concentration in the routine blood chemistry suggesting chronic respiratory acidosis. A chest x-ray may be helpful if pneumonia is suspected. Because myocardial infarction can present with altered mental status in the setting of cardiogenic embolism or systemic hypotension, an ECG should be considered.

SUBSEQUENT EVALUATION

If the cause of altered mental status is not apparent after the initial workup, additional testing may be necessary because of the large variety of treatable etiologies (Table 1-2). However, an extensive workup for altered mental status is expensive, can cause iatrogenic complications, and may be unnecessary in some cases. Therefore, appropriate selection of patients for further workup is critical.
For patients with delirium with clear risk factors and an obvious precipitant, workup beyond the initial approach described above may not be necessary. Delirium is theorized to occur in the setting of decreased cerebral reserve, resulting in diminished capacity to withstand a variety of insults that can trigger the acute confusional state. Advanced age and pre-existing cognitive dysfunction are the most consistently identified risk factors for delirium in prospective studies.\(^{12,13}\)

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**TABLE 1-2** Commonly Cited Etiologies of Altered Mental Status

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiologies</th>
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<tbody>
<tr>
<td>Vascular</td>
<td>Ischemic stroke(^a)&lt;br&gt;Intracerebral or subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Infectious</td>
<td>Urinary tract infection&lt;br&gt;Pneumonia&lt;br&gt;Sepsis&lt;br&gt;Encephalitis&lt;br&gt;Meningitis</td>
</tr>
<tr>
<td>Toxic</td>
<td>Intoxication and overdose&lt;br&gt; Withdrawal (alcohol, benzodiazepines, barbiturates, heroin)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Concussion&lt;br&gt;Subdural hematoma</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Neuropsychiatric lupus&lt;br&gt;Behçet syndrome&lt;br&gt;Vasculitis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Electrolytes&lt;br&gt; Hyponatremia/hypernatremia&lt;br&gt; Hypercalcemia&lt;br&gt; Hypermagnesemia&lt;br&gt; Hypophosphatemia</td>
</tr>
<tr>
<td>Seizure-Related</td>
<td>Postictal state&lt;br&gt; Nonconvulsive status epilepticus</td>
</tr>
<tr>
<td>Degenerative</td>
<td>Dementia with Lewy bodies&lt;br&gt; Prion disease</td>
</tr>
<tr>
<td>Psychiatric Disease-Related</td>
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\(^a\)Vascular lesions rarely lead to isolated delirium in the absence of other neurologic signs; rare exceptions include lesions of the thalamus and nondominant posterior parietal lobe.

\(^b\)A recent study implicates LGI1 as the antigen in limbic encephalitis previously attributed to VGKC antibodies. Because LGI1 coprecipitates with VGKC, it is likely the commercial test for VGKC antibodies is actually detecting antibodies of LGI1. However, because direct testing for LGI1 antibodies is not yet available and because other disorders are associated with VGKC antibodies (eg, Morvan syndrome), it is still appropriate to order the commercial test for VGKC antibodies in patients with limbic encephalitis.\(^{11}\)
Additional risk factors for delirium are listed in Table 1-3. Although some types of neurodegenerative disease, such as Lewy body dementia, may cause delirium in and of themselves, most patients with dementia exhibit normal levels of arousal and attention until the very late stages of disease. Occasionally prion disease may progress rapidly enough to present with encephalopathy. The insults that can precipitate delirium include a wide range of pathologic conditions (Table 1-2), many of which may cause encephalopathy in patients without risk factors, and iatrogenic insults that the patient with sufficient cognitive reserve can usually withstand (Table 1-3). If a patient without known underlying neurologic disease becomes delirious with a relatively innocuous insult such as a urinary tract infection, follow-up should be arranged with neurology to screen for an underlying process such as an incipient neurodegenerative disease. These patients have essentially failed a “stress test for the brain,” and an underlying disorder should be sought.

Delirium tends to improve steadily once the precipitant is removed or treated; if a patient does not show gradual improvement, the diagnosis should be revisited. In patients without a clear precipitant, even if they have predisposing risk factors for delirium, further workup may be warranted. Patients without risk factors for delirium and those at high risk for intracranial infection or neoplasm generally require further workup as well. This is discussed in more detail below.

**Neuroimaging**

Brain imaging, at least with noncontrast CT, is mandatory in patients with altered mental status who also have focal neurologic deficits or seizures. A head CT is also recommended prior to performing a lumbar puncture. Other situations in

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**TABLE 1-3** Delirium Risk Factors and Iatrogenic Precipitants

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Age &gt; 70 years</td>
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<tr>
<td>Dementia or mild cognitive impairment</td>
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<tr>
<td>Vision impairment (usually less than 20/70 with correction)</td>
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<tr>
<td>Hearing impairment</td>
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<tr>
<td>Functional limitation</td>
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<tr>
<td>Alcohol abuse</td>
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<tr>
<td>Malnutrition (indicated by an albumin &lt; 2 g/dL)</td>
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<tr>
<td>Dehydration (indicated by a blood urea nitrogen/creatinine ratio &gt; 18)</td>
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<table>
<thead>
<tr>
<th>Iatrogenic Precipitants</th>
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<tbody>
<tr>
<td>Use of restraints</td>
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<tr>
<td>Urinary catheters</td>
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<tr>
<td>Multiple procedures</td>
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<tr>
<td>Sleep deprivation</td>
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<tr>
<td>Untreated pain</td>
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<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Anticholinergics</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Opiates</td>
</tr>
<tr>
<td>Antihistamines</td>
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<tr>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Muscle relaxants</td>
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<tr>
<td>Dopamine agonists</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Levodopa</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Fluoroquinolone and cephalosporin antibiotics</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Digitalis</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Thoracic (cardiac and noncardiac)</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Hip replacement</td>
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</tbody>
</table>
which the likelihood of intracranial pathology is high also mandate brain imaging. Examples include patients with a previous brain lesion, recent trauma, HIV, a history of organ transplantation or other immunocompromised state, or a history of cancer. Whether brain imaging should be routinely obtained in patients with encephalopathy without focal neurologic signs or the aforementioned risk factors is more controversial.

Several attempts have been made to study the yield of brain imaging in patients with altered mental status. In emergency department patients without head trauma, altered mental status is one of four clinical characteristics that predict an abnormal CT scan with high sensitivity (the others being headache with vomiting, age greater than 60 years, and focal neurologic deficits). In one study, 13% of 181 patients with altered mental status had a clinically significant finding on head CT. In a more recent study of 294 patients admitted to an inpatient neurology service with acute confusion of unclear etiology, 14% had a clinically significant finding on either CT or MRI. Although most patients without focal neurologic deficits had normal scans, half of those with findings on brain imaging had no focal neurologic signs; these included patients with ischemic stroke, encephalitis, and hydrocephalus. Conversely, in a study of 106 consecutive CT scans performed in an emergency department for acute confusion in patients over age 70, all abnormal scans were in patients with either focal neurologic findings or recent trauma. However, because MRI was not used as a criterion standard in this study, it is possible some intracranial lesions were missed.

Although strokes causing altered mental status are almost always accompanied by focal deficits, especially upon careful neurologic examination, occasionally such localizing signs are absent (Case 1-1). Specific types of infarction that may cause such a scenario include thalamic infarctions in the paramedian territory, nondominant parietal lobe infarctions, and diffuse bihemispheric or watershed infarctions caused either by a proximal embolic source or a proximal embolic source. Specific types of infarction that may cause such a scenario include thalamic infarctions in the paramedian territory, nondominant parietal lobe infarctions, and diffuse bihemispheric or watershed infarctions caused either by a proximal embolic source or a proximal embolic source.

**Case 1-1**

A 55-year-old right-handed man was brought to the hospital with confusion. Two weeks ago, he experienced the sudden onset of fluctuating disorientation and forgetfulness. He also had exhibited strange behaviors such as attempting to turn the television on with his cell phone. He underwent a right anterior temporal lobectomy 3 years ago for medically refractory epilepsy but still had one complex partial seizure per month. His last seizure was 10 days prior to presentation. He had also experienced a steady decline in memory and concentration associated with parkinsonism over the past 8 years. His medications included carbamazepine, divalproex, levetiracetam, memantine, venlafaxine, quetiapine, and tamsulosin. On examination he was awake but demonstrated psychomotor slowing, disorientation, and impaired attention and short-term recall. His gait was wide based and mildly unsteady, but otherwise his neurologic examination was normal.

Basic laboratory testing and urinalysis were normal. Carbamazepine and valproic acid levels were in the therapeutic range. CT of the brain showed a remote lacunar infarct in the left internal capsule and the right temporal resection cavity.

Continued on page 974
Diffuse cerebral vasculopathy. Exemplifying the last-mentioned is a series of eight patients with encephalopathy after coronary artery bypass grafting surgery who received brain MRI, seven of whom had multiple bilateral infarctions on diffusion-weighted imaging. Three of these patients had no focal deficits when examined by a neurologist, and no alternative explanation for their encephalopathy could be found.

Posterior reversible encephalopathy syndrome (PRES) is another important cause of altered mental status that may present without focal deficits and is diagnosed by MRI. Patients usually present with diffuse encephalopathy, and most also have seizures; hemiparesis or visual field deficits occur in fewer than half of patients. The diagnosis is suspected in the setting of eclampsia, hypertensive emergency, or immunosuppression with calcineurin inhibitors, although a number of other medical conditions have been associated with PRES. Typical MRI findings include relatively symmetric, patchy, and confluent hyperintensities on T2-weighted images in the occipital and parietal white matter, although atypical features are common, including frontal, brainstem, and cortical involvement.

In conclusion, if the cause of altered mental status is not obvious after the initial evaluation, brain imaging with at

Comment. This patient presented to the hospital with a 2-week history of delirium. He had no focal findings on neurologic examination, and his preexisting cognitive dysfunction is a major risk factor for delirium. He is taking numerous medications known to cause delirium; however, no recent changes in dosage had been made. Thus, because no obvious precipitant for delirium exists, a more extensive workup is warranted.

Because encephalitis can present with subacute delirium, a lumbar puncture should be performed. Empiric treatment with acyclovir is reasonable until a herpes simplex virus PCR is negative. Serum ammonia can be checked, given the possibility of encephalopathy due to valproic acid. A vitamin B12 level and thyroid function tests are also reasonable. Given the history of epilepsy, an extended EEG should be performed to rule out nonconvulsive status epilepticus. Finally, an MRI can be diagnostic in cases of otherwise unexplained encephalopathy. In this case, additional laboratory studies were normal and the EEG showed only a right-sided breach rhythm with intermittent temporal sharps but no seizures. An MRI showed a subacute infarction in the left anteromedial thalamus (Figure 1-1).

**FIGURE 1-1** A, diffusion-weighted image. B, fluid-attenuated inversion recovery sequence.
least noncontrast CT is indicated. While the yield of brain imaging in the absence of trauma or a focal neurologic deficit is likely low, especially in elderly patients who are at higher risk for metabolic encephalopathy, it is still possible to find a clinically important lesion. MRI may be especially useful in such situations. **Case 1-2** is illustrative of this point.

### Lumbar Puncture

**Whether to perform a lumbar puncture in a patient with altered mental status depends on whether the change in mental status developed before or during the hospitalization, because nosocomial meningitis is very uncommon. In two series comprising 121 medical and surgical inpatients who underwent lumbar puncture to rule out nosocomial meningitis.**

<table>
<thead>
<tr>
<th>KEY POINT</th>
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<tbody>
<tr>
<td>Immunocompetent patients without a history of neurosurgery or head trauma who develop altered mental status during their hospitalization are unlikely to have meningitis.</td>
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</table>

#### Case 1-2

An 83-year-old right-handed woman presented to the emergency department with vertigo, numbness, and weakness. Her symptoms started 3 days ago with vertigo and numbness in the feet, followed by dysarthria and weakness that progressed to the point where she could no longer stand. She had been taking metronidazole for the past month for a *Clostridium difficile* infection. In the emergency department she was awake but slow to respond and diffusely weak; a CT scan showed diffuse atrophy and remote bilateral basal ganglia lacunar infarcts. Basic laboratory evaluation showed mild renal dysfunction with a blood urea nitrogen of 50 mg/dL and a creatinine of 1.5 mg/dL. Urinalysis suggested a urinary tract infection. She was admitted to the hospital and started on cefazolin. Over the next 24 hours she became progressively less responsive. A neurology consultation was obtained.

On neurologic examination, she sluggishly opened her eyes to painful stimuli but showed no other motor response to central or peripheral pain and did not follow any commands. Brainstem reflexes were intact. Tone and reflexes were normal, with the exception of absent ankle jerks, and plantar responses were flexor.

**Comment.** This elderly patient was unresponsive with a nonfocal neurologic examination at the time of consultation. She had a urinary tract infection and mild renal failure, which could lead to encephalopathy in an elderly patient. However, the history of vertigo, dysarthria, and bilateral weakness and numbness preceding the onset of unresponsiveness is suggestive of brainstem localization. The gradual progression of symptoms over days makes stroke unlikely, but progressive basilar artery ischemia should be ruled out with an MRI and magnetic resonance angiography. A lumbar puncture and EEG would also be reasonable if the patient does not improve with treatment of her urinary tract infection.

In this case, the MRI showed symmetric T2 prolongation in the bilateral dentate nuclei (**Figure 1-2A**), middle cerebellar peduncles, dorsal pons, red nuclei (**Figure 1-2B**), splenium of the corpus callosum, and bilateral centrum semiovale. A lumbar puncture was normal. These findings have been described in Wernicke encephalopathy and with metronidazole toxicity. The patient was treated with IV thiamine and her metronidazole was discontinued; she showed gradual clinical improvement. This case illustrates the importance of MRI in the workup of otherwise unexplained delirium and the need to always carefully review all of a patient’s medications.
meningitis, no cases were found.\textsuperscript{24,25} Thus, in the absence of additional features of CNS infection such as fever, headache, or neck stiffness, lumbar puncture is of low yield in most patients with hospital-acquired delirium. However, this conclusion should not be generalized to patients with head trauma, neurosurgical procedures or devices, or HIV or other immunocompromised states.

For patients who present to medical attention with altered mental status, the threshold for performing a lumbar puncture should be lower. While bacterial meningitis is unlikely in immunocompetent patients with encephalopathy in the absence of fever or neck stiffness (95% of patients in a pooled analysis had at least two of the three cardinal manifestations of meningitis: encephalopathy, fever, and neck stiffness), lumbar puncture can diagnose other causes of altered mental status that may not cause fever as frequently, such as tuberculous or fungal meningitis, aseptic meningitis, or carcinomatous meningitis (Table 1-4).\textsuperscript{26} Indeed, the absence of fever may not be sensitive enough to justify foregoing lumbar puncture. In a recent retrospective study, Shah and colleagues found no significant difference between afebrile and febrile patients in the frequency of CSF pleocytosis (18% and 24%, respectively).

In cases of meningitis, the CSF may rarely be only mildly abnormal within the first 24 hours of illness.\textsuperscript{28} Therefore, a lumbar puncture should be repeated if clinical suspicion remains high. The CSF may also lack a pleocytosis in as many as 10% of cases of encephalitis.\textsuperscript{29} Because early treatment significantly reduces morbidity and mortality of herpes simplex virus (HSV) encephalitis, it is reasonable to have a low threshold to start acyclovir and test for HSV-1.

\begin{table}[h]
\centering
\caption{CSF Studies That May Be Helpful in the Workup of Unexplained Altered Mental Status}
\begin{tabular}{|l|}
\hline
\textbf{All Patients} \\
Red and white blood cell count with differential, protein, and glucose \\
Bacterial culture \\
PCR for HSV-1, HSV-2, and VZV \\
\textbf{When Encephalitis is Suspected}\textsuperscript{11} \\
Viral PCRs \\
HSV-1 \\
HSV-2 \\
VZV \\
Enterovirus \\
WNV \\
EBV\textsuperscript{a} \\
IgG and IgM for WNV\textsuperscript{b}, St. Louis encephalitis\textsuperscript{b}, and EBV; additional viral serologies may be considered depending on season, exposures, and geography \\
Bacterial PCRs \\
\textit{Tropheryma whippelii} \\
\textit{Bartonella genus} \\
Some rickettsioses\textsuperscript{b} \\
Venereal Disease Research Laboratory and \textit{Borrelia burgdorferi} ELISA and Western blot\textsuperscript{b} \\
Acid-fast bacilli smear and culture, \textit{Mycobacterium tuberculosis} PCR\textsuperscript{c} \\
Fungal culture \\
\textit{Cryptococcus} antigen, \textit{Histoplasma} antigen\textsuperscript{b}, \textit{Coccidioides} immunodiffusion or complement fixation\textsuperscript{b} \\
IgG index and oligoclonal bands \\
Testing for antibodies associated with paraneoplastic and autoimmune limbic encephalitis \\
\textbf{Patients With a History of Malignancy} \\
Cytology and flow cytometry \\
\textbf{Patients Who Are Immunocompromised} \\
PCR for cytomegalovirus, human herpesvirus 6, JC virus \\
Galactomannan if aspergillosis is suspected \\
\hline
\end{tabular}
\end{table}

HSV-1 = herpes simplex virus, type 1; HSV-2 = herpes simplex virus, type 2; VZV = varicella-zoster virus; WNV = West Nile virus; EBV = Epstein-Barr virus; Ig = immunoglobulin.
\textsuperscript{a}Can be falsely positive because of blood contamination; should be performed with serologic testing.
\textsuperscript{b}Depends on season, geographic location, and travel history.
\textsuperscript{c}Diagnostic yield is increased with samples of higher volume; tuberculosis PCR has low sensitivity.
and HSV-2 DNA with PCR in patients with altered mental status and fever, even in the absence of CSF abnormalities. The CSF PCR is 95% sensitive for HSV when performed between 72 hours and 10 days of illness onset; the test should be repeated in cases where the clinical suspicion is high or the lumber puncture was performed early in the course (Case 1-3).

Special care must be taken to rule out infection in immunocompromised patients with altered mental status. Patients with HIV are at risk for meningitis due to Cryptococcus, tuberculosis, pyogenic bacteria, syphilis, and cytomegalovirus (CMV) ventriculoencephalitis, especially when their CD4 count falls below 200 cells/mm³. Although toxoplasmosis and primary CNS lymphoma usually present with focal deficits, multifocal disease can occasionally present with diffuse encephalopathy. In addition to common bacterial and viral pathogens, organ and bone marrow transplant recipients are at high risk for CNS infection with less common organisms, including CMV, varicella-zoster virus, human herpesvirus

KEY POINT
- The CSF may lack a pleocytosis in 10% of cases of encephalitis. Clinicians should have a low threshold to start empiric treatment with acyclovir and test for herpes simplex virus with CSF PCR in patients with altered mental status and fever or seizures.

Case 1-3
A 59-year-old right-handed man was brought to the emergency department for altered mental status. Ten days ago he reported experiencing a headache and forgetfulness. On the morning of admission, he developed nonsensical speech and an ambulance was called. He has a history of HIV with a CD4 count of 158 cells/mm³, and he is blind because of cytomegalovirus (CMV) retinitis. In the emergency department he had a witnessed generalized seizure beginning with right gaze deviation. The seizure was controlled with lorazepam, and a noncontrast head CT was normal. He was intubated for airway protection and admitted to the medical intensive care unit.

Comment. In patients with HIV with altered mental status and seizure, especially those with a CD4 count below 200 cells/mm³, a variety of infectious and noninfectious etiologies must be considered. Opportunistic infections of the CNS that predispose to seizures include toxoplasmosis and meningoencephalitis due to tuberculosis, syphilis, cryptococcus, or CMV. Of course, these patients are also at risk for more common infections that are not limited to the immunocompromised host, such as bacterial meningitis, brain abscess, and herpes simplex virus (HSV) and varicella-zoster virus encephalitis. Noninfectious CNS diseases to be considered in patients with HIV include primary CNS lymphoma and cerebrovascular disease due to the accelerated atherosclerosis seen with protease inhibitors. Progressive multifocal leukoencephalopathy is less likely to present with seizures or altered mental status and more likely to present with focal deficits.

In this case, a lumbar puncture revealed a lymphocytic pleocytosis and elevated protein. Empiric therapy with antibiotics and acyclovir was begun. An MRI showed T2 hyperintensity with mild mass effect and enhancement in the left medial temporal lobe (Figure 1-3). Culture of CSF and PCR for HSV, varicella-zoster virus, and CMV were negative, as were the rapid plasma reagin and cryptococcal antigen. Antibiotics were discontinued, but given the high suspicion for HSV encephalitis, acyclovir was continued. A repeat HSV PCR on CSF drawn 3 days later was positive. It is important to keep in mind that HSV PCR is only 95% sensitive; if clinical suspicion is high, patients should be treated empirically and the test should be repeated on a fresh CSF sample.
Aspergillus, and Nocardia. Diagnosis relies on CSF PCR for viral organisms and often direct culture for invasive fungal and atypical bacterial species. Some emerging data suggest that CSF galactomannan may be a sensitive marker for CNS aspergillosis in patients who are immunocompromised.32

Over the last decade it has become apparent that many cases of previously undiagnosed encephalitis are associated with antibodies to neuronal antigens. In some cases a putative autoimmune etiology exists, and in other cases the illness is paraneoplastic. A recent population-based study from England found 8% of cases of encephalitis over a 2-year period were associated with antibodies to NMDA receptors or what was formerly thought to be voltage-gated potassium channels.33 The MRI is often normal in such cases, but the CSF is usually inflammatory.34 In a large series of paraneoplastic neurologic syndromes from a European registry, 93% had elevated CSF protein, white blood cell count, or oligoclonal bands.35 Importantly, in 10% of cases the only abnormality was the presence of oligoclonal bands unique to the CSF. For this reason, it may be helpful to check immunoglobulin G index and oligoclonal bands in patients with suspected encephalitis. If evidence of inflammation exists, further workup for an occult neoplasm and antibody testing on serum and CSF may be warranted.

Neoplastic metastases to the subarachnoid space resulting in carcinomatous meningitis often present with encephalopathy with or without concomitant cranial neuropathies or radiculopathies. Cancers that most frequently metastasize to the leptomeninges include breast, lung, melanoma, lymphoma, and leukemia.36 While MRI may be suggestive and even diagnostic in some cases, CSF cytology is often required to make the diagnosis.

Electroencephalography
Seizures must be considered in patients with unexplained encephalopathy. Several prospective studies have found an incidence of seizures in 10% to 19% of such patients, with the higher rates reflecting patients in the intensive care unit.37,38 Although repetitive motor activity, nystagmus, or gaze deviation may increase the likelihood of a positive EEG, the absence of such findings does not rule out underlying nonconvulsive electrical activity, making EEG an essential diagnostic tool.39,40 Some studies suggest that 24 hours of recording to capture seizure activity has a higher degree of sensitivity than a brief recording.37

Serum Laboratory Studies
Several endocrine abnormalities may cause altered mental status. Hyperthyroidism commonly leads to psychiatric symptoms such as mania, depression, and anxiety, although abnormalities on neuropsychiatric testing, aside from attentional deficits, are rarely encountered.41 Severe thyrotoxicosis, however, may lead to delirium. Hypothyroidism can cause significant cognitive dysfunction or even stupor or coma when severe.42 Measurement of thyroid-stimulating hormone and free thyroxine confirms the diagnosis. Cushing syndrome, due to either endogenous or iatrogenic cortisol excess, may lead to psychosis or delirium. Psychosis or delirium may also be the presenting feature of addisonian crisis.43 Additional metabolic studies that should be undertaken in the patient with encephalopathy include measurement of vitamin B12 and ammonia. Deficiency of vitamin B12 has long been associated with both subacute cognitive decline and delirium. Hyperammonemia is associated with altered mental status in several conditions in addition to hepatic disease. For example, valproic acid can lead to hyperammonemic
encephalopathy in both children and adults.\textsuperscript{44} Occasionally the serum ammonia may be normal but the CSF glutamine may be elevated.\textsuperscript{45} This can occur with serum valproic acid levels in the therapeutic range and is potentiated by the coadministration of topiramate. Patients with cirrhosis are prone to hyperammonemia and hepatic encephalopathy due to acquired portal-systemic shunting, but congenital and acquired portal-systemic shunts can also lead to the same condition in patients without overt liver disease.\textsuperscript{46,47} Transrectal portal scintigraphy or angiographic studies of the portal circulation may be necessary to demonstrate the shunt. Finally, very rarely a urea cycle deficit may present during adulthood.

Occasionally, the presence of an offending toxin or drug is not obvious from the initial history or the standard urine toxicology screen available in the emergency department. It is often helpful to revisit the history with family members and friends to identify potential ingestions. Over-the-counter and herbal medications should be reviewed thoroughly in addition to prescription medications (Table 1-5). An extended toxicology screen may also be helpful.

In addition to paraneoplastic and autoimmune limbic encephalitis, several other autoimmune diseases may present with encephalopathy, and serum autoantibody testing may be diagnostically helpful in such patients. Among the wide array of neurologic symptoms that can complicate systemic lupus erythematosus, acute confusional states and psychosis are uncommon but well described, occurring in as many as 40% of patients with lupus in some series.\textsuperscript{48} Markers of disease activity such as complement levels, antinuclear antibodies, and double-stranded DNA should be elevated in active lupus; CSF analysis is useful in working up other causes of encephalopathy but is often normal in active neuropsychiatric lupus.\textsuperscript{49} Autoimmune encephalitis has been reported with Sjögren syndrome but is very rare.\textsuperscript{50} Other connective tissue diseases may cause altered mental status through an ischemic mechanism due to either vasculitis in most cases or thrombosis (arterial or venous) in antiphospholipid antibody syndrome.

Hashimoto encephalitis is a noninfectious, nonvasculitic encephalitis associated with antithyroglobulin and antithyroidperoxidase antibodies that usually responds to steroid treatment. Given the high incidence of antithyroid antibodies in the general population, it is unlikely they play a causative role in this disorder; it is also unlikely their frequent occurrence in steroid-responsive encephalopathy is incidental.\textsuperscript{51} Other proposed names for this condition include steroid-responsive encephalopathy with autoimmune thyroiditis and nonvasculitic autoimmune meningoencephalitis; no single term has yet gained wide acceptance. Given the responsiveness of the condition to steroids, testing for antithyroid antibodies remains an important part of the workup for an otherwise unexplained encephalopathy.

**PREVENTION, TREATMENT, AND FOLLOW-UP**

Treatment of altered mental status should focus on the underlying cause. Specific treatment for the conditions discussed here is beyond the scope of this article. In cases of encephalopathy in which an underlying cause cannot be determined, treatment is largely supportive. Potentially offending medications should be discontinued, bladder catheters should be removed as soon as possible, and family members or sitters should be used in lieu of restraints to ensure patient safety. Pharmacologic treatment of altered mental status should be avoided, given the potential for new medications to precipitate or worsen delirium. In
# Table 1-5

<table>
<thead>
<tr>
<th>Commonly Prescribed Drugs Implicated as Causes of Altered Mental Status&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Drugs With Class Effect</strong></td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Antihistamines (including H2 blockers such as cimetidine and famotidine)</td>
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<tr>
<td>Antipsychotics (via sedative effects or neuroleptic malignant syndrome)</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Calcineurin inhibitors</td>
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<tr>
<td>Cephalosporins (especially in the setting of renal failure)</td>
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<tr>
<td>Dopamine agonists and levodopa</td>
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<tr>
<td>Fluoroquinolones</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>Muscle relaxants (if centrally acting)</td>
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<tr>
<td>Opiates</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
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<tr>
<td><strong>Drugs Without Class Effect</strong></td>
</tr>
<tr>
<td>Antiemetics</td>
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<tr>
<td>Antihypertensives</td>
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<tr>
<td>Clonidine</td>
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<tr>
<td>Nifedipine</td>
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<tr>
<td>Antidepressants</td>
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<tr>
<td>Bupropion</td>
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<tr>
<td>Mirtazapine</td>
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<tr>
<td>Paroxetine</td>
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<tr>
<td>Trazodone</td>
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<tr>
<td>Antifungal agents</td>
</tr>
<tr>
<td>Micafungin</td>
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<tr>
<td>Voriconazole</td>
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<tr>
<td>Posaconazole</td>
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</tbody>
</table>

<sup>a</sup>Many other medications have been reported to cause confusion, delirium, or encephalopathy with varying degrees of evidence implicating causality. In any patient with delirium, a careful review of all prescription and nonprescription medications is advised.

cases in which sedative medications are required for patient safety, however, low doses of antipsychotics are considered first-line agents, although they are not approved by the US Food and Drug Administration (FDA) for this indication.\textsuperscript{52} Caveats to their use include the FDA black box warning regarding increased mortality among elderly patients with dementia, their potential to prolong the overall length of an episode of delirium while temporarily relieving symptoms, and their potential for profoundly sedating and extrapyramidal effects in patients with Lewy body dementia. Benzodiazepines should be avoided, except in cases of alcohol withdrawal, given their potential to exacerbate symptoms of delirium. A recent Cochrane Review found no studies supporting their use in non-alcohol withdrawal delirium.\textsuperscript{53}

In some patients, prevention of delirium may be possible by nonpharmacologic means. A 2007 Cochrane Review identified only six prospective randomized trials investigating prevention of postoperative delirium.\textsuperscript{54} Five of these studies examined pharmacologic interventions, including haloperidol, donepezil, diazepam, cytidine diphosphocholine, and epidural versus halothane anesthesia; only haloperidol showed promise in reducing the length and severity of delirium episodes, although the overall number was no different between groups. The sixth study demonstrated that a proactive geriatrics consultation reduced the incidence of postoperative delirium from 50% to 32% among hip surgery patients. In a separate study not included in the Cochrane Review, a multicomponent intervention using environmental and nursing strategies reduced the incidence of hospital-acquired delirium from 15% to 9.9% in high-risk medical patients.\textsuperscript{55}

Critically ill patients are at especially high risk for developing delirium.\textsuperscript{5 Not only are they ill with conditions that can precipitate delirium and encephalopathy, in order to relieve the discomfort of mechanical ventilation they are also exposed to various sedative medications that are known causes of delirium. Recently a new selective α\textsubscript{2} agonist, dexmedetomidine, has shown promise in reducing delirium while maintaining adequate sedation in critically ill patients who are mechanically ventilated. In three separate randomized trials, dexmedetomidine outperformed lorazepam, midazolam, and morphine by reducing the prevalence of delirium during intubation and reducing ventilator time from 5.6 to 3.7 days compared with midazolam.\textsuperscript{56–58}

For patients with altered mental status of any cause, follow-up with a neurologist is important because it often takes time for cognitive function to normalize, if it does at all, and issues regarding cognitive disability often need to be addressed. Patients with delirium are also at high risk for developing dementia and should be reevaluated in the outpatient setting.\textsuperscript{59} This will become especially important once preventive and treatment strategies for neurodegenerative diseases are developed, because delirium may become one way of identifying incipient cases of mild cognitive impairment or dementia.

**REFERENCES**


**KEY POINTS**

- Symptomatic treatment of altered mental status and delirium should focus on nonpharmacologic measures, with medications held in reserve unless required for patient safety. Benzodiazepines should be used only in cases of alcohol withdrawal.
- A multicomponent intervention using frequent reorientation, provision of vision and hearing aids, normalization of sleep-wake cycles, early mobilization, and hydration for patients with signs of dehydration may be effective in preventing delirium.


