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Case 39-2012: A 55-Year-Old Man with Alcoholism, Recurrent Seizures, and Agitation

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PRESENTATION OF CASE

Dr. Benjamin C. Silverman (Psychiatry): A 55-year-old man with a history of alcoholism was admitted to the medical intensive care unit (ICU) at this hospital because of seizures and agitation.

One day before admission, the patient discontinued his daily consumption of alcohol in preparation for a family event. On the day of admission, generalized tonic–clonic movements developed and resolved spontaneously after 1 minute. During the episode, he was caught while falling; he had no head trauma. On examination by emergency medical services personnel, he was oriented to person, place, and time. The blood pressure was 160/110 mm Hg, the pulse 88 beats per minute and regular, and the respiratory rate 16 breaths per minute. The patient had dilated pupils, slurred speech, and diaphoresis. There was no evidence of incontinence. Oxygen was administered through a nonrebreather face mask at a rate of 15 liters per minute. A capillary glucose level was 135 mg per deciliter. He was brought to the emergency department at this hospital.

The patient reportedly drank one case of beer daily. Nine years earlier, he had had a seizure related to alcohol withdrawal. Approximately 3.5 years earlier, he was found on the street intoxicated, with a fractured mandible; he was admitted to another hospital, and delirium and agitation associated with alcohol withdrawal developed during admission. He had asthma, hypertension, atrial fibrillation, congestive heart failure, and coronary artery disease; in the past, he had undergone coronary-artery bypass grafting and aortic-valve replacement with a porcine valve and had had *Klebsiella pneumoniae* infection. A skin test was positive for tuberculosis 4 years earlier. The patient had taken cardiac and antihypertensive medications in the past; current medications were unknown. He had no known allergies. He lived with his girlfriend and had previously been homeless. He had been smoking cigarettes for many years; it was not known whether there was a history of illicit drug use. His father had died of heart disease, and there was a family history of diabetes mellitus.

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On examination, the patient was confused and afebrile. The blood pressure was 140/84 mm Hg, the pulse 75 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while he was breathing oxygen through a nonrebreather face mask. The pupils were 2 mm in diameter and reactive; the remainder of the examination was normal. Computed tomography (CT) of the head without the administration of contrast material revealed nonspecific periventricular hypodensities and prominent ventricles and sulci, features that were consistent with mild generalized volume loss; there was no evidence of acute infarction or hemorrhage. A chest radiograph showed clear lungs, with cardiac enlargement and postoperative changes that were stable as compared with 4 years previously.

Approximately 4.5 hours after the patient's arrival, generalized tonic–clonic movements recurred, along with urinary incontinence. Lorazepam was administered intravenously, with resolution of seizure activity. The partial-thromboplastin time, blood levels of glucose and lipase, and results of renal-function tests were normal, and screening of the blood for toxins was negative; other results of laboratory tests are shown in Table 1. During the next 2 hours, increasing agitation and confusion occurred, with incoherent speech, diaphoresis, and combative behavior that required the use of restraints. Lorazepam, haloperidol, magnesium sulfate, and intravenous fluids were administered, which led to eventual sedation and decreased agitation; the trachea was intubated for airway protection, propofol was administered, and a urinary catheter was placed. An electrocardiogram revealed atrial fibrillation, with a ventricular rate of 135 beats per minute and nonspecific ST-segment and T-wave changes. Urinalysis revealed trace occult blood, 0 to 2 red cells per high-power field, and mucin; screening of the urine (after the administration of lorazepam) revealed cannabinoids and benzodiazepines.

The patient was admitted to the medical ICU. On admission, the temperature was 37.4°C, the blood pressure 136/85 mm Hg, the mean arterial pressure 100 mm Hg, and the pulse 110 beats per minute. The patient was sedated and intubated. There were no other focal abnormalities on examination. During the next 2 days, levels of cardiac enzymes and isoenzymes were normal and testing for antibodies against heparin–platelet factor 4 complexes was negative; other test results are shown in Table 1. Lorazepam and propofol were continued, and diazepam, folate, thiamine, aspirin, atenolol, dalteparin, multivitamins, magnesium sulfate, potassium phosphate, and normal saline were administered. As the dose of propofol was gradually decreased, agitation increased and the respiratory rate rose to 40 breaths per minute; the dose of propofol was increased, with improvement.

On the third day, management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Felicia A. Smith: I am aware of the diagnosis. This man presented with seizures, altered mental status, and autonomic instability after he stopped drinking alcohol, 1 day before presentation. Although this presentation is consistent with acute alcohol withdrawal, other diagnoses should also be considered and other causes of seizures and altered mental status should be ruled out. The differential diagnosis of altered mental status with seizures consists of two basic categories — intrinsic seizures (as in epilepsy) and acute symptomatic seizures (i.e., provoked seizures). Since this patient does not have a known history of epilepsy, we must consider the causes of provoked seizures, including acute neurologic illness (e.g., stroke, traumatic brain injury, meningitis or encephalitis, or anoxia); acute medical illness, such as metabolic derangement (e.g., hypoglycemia, hyponatremia, or hypocalcemia); and intoxication or a withdrawal state.[1] Initial laboratory studies are not suggestive of clinically significant metabolic derangement. The patient is afebrile and has no signs of meningitis or encephalitis. Likewise, oxygen saturation is normal and not suggestive of an anoxic event. The patient's history is not consistent with acute traumatic brain injury. A head CT was performed to assess for other acute central nervous system processes.

May we review the radiologic studies?

Dr. Pamela W. Schaefer: CT images of the brain obtained without the administration of contrast material show no evidence of acute ischemia, intracranial hemorrhage, edema, mass lesion, or mass effect. There is more tissue loss than would be expected for the patient's age, with focal tissue loss in the cerebellum. There is also mild peri-

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation, Emergency Department	7 Hr Later, Intensive Care Unit
Hematocrit (%)	41.0–53.0 (men)	42.5	32.7
Hemoglobin (g/dl)	13.5–17.5 (men)	13.8	10.7
White-cell count (per mm^3)	4500–11,000	4700	4700
Differential count (%)			
Neutrophils	40–70	81	76
Lymphocytes	22–44	12	15
Monocytes	4–11	6	7
Eosinophils	0–8	0	2
Platelet count (per mm^3)	150,000–400,000	136,000	109,000
Prothrombin time (sec)	10.8–13.4	14.0	14.6
International normalized ratio for prothrombin time		1.2	1.3
Sodium (mmol/liter)	135–145	139	135
Potassium (mmol/liter)	3.4–4.8	3.7	2.9
Chloride (mmol/liter)	100–108	100	102
Carbon dioxide (mmol/liter)	23.0–31.9	31.7	27.1
Bilirubin (mg/dl)			
Total	0.0–1.0	1.3	1.3
Direct	0.0–0.4	0.3	0.4
Protein (g/dl)			
Total	6.0–8.3	7.1	5.6
Albumin	3.3–5.0	4.2	3.4
Globulin	2.6–4.1	2.9	2.2
Calcium (mg/dl)	8.5–10.5	9.5	7.8
Magnesium (mmol/liter)	0.7–1.0	0.7	0.8
Phosphorus (mg/dl)	2.6–4.5	1.4	1.5
Alkaline phosphatase (U/liter)	45–115	131	97
Aspartate aminotransferase (U/liter)	10–40	89	64
Alanine aminotransferase (U/liter)	10–55	42	30
Amylase (U/liter)	3–100	190	161

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

ventricular hypoattenuation, a feature consistent with mild microvascular ischemic change. These findings are common in patients with long-standing alcoholism. A chest radiograph shows stable, mild cardiac enlargement and clear lungs.

Dr. Smith: Since the CT image of the head is not suggestive of an acute process, the most likely diagnosis is intoxication or a withdrawal state or both. The patient had the alcohol withdrawal syndrome, complicated by seizure, 9 years previously; the family reports that he currently drinks a case of beer daily. Moreover, he stopped drinking 24 to 36 hours before presentation. In the emergency department, he had tachycardia and hypertension and was agitated and confused. Toxicologic screening revealed the presence of

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cannabinoids and benzodiazepines. This presentation is most consistent with the alcohol withdrawal syndrome complicated by seizure and delirium.

CLINICAL DIAGNOSIS

The alcohol withdrawal syndrome.

DR. FELICIA A. SMITH'S DIAGNOSIS

Delirium due to alcohol withdrawal or multifactorial delirium.

DISCUSSION OF MANAGEMENT

ALCOHOL WITHDRAWAL SYNDROMES

Dr. Shamim H. Nejad: At admission, this patient had a history of at least two previous episodes of alcohol withdrawal delirium (also known as delirium tremens), in addition to several episodes of seizures related to alcohol withdrawal. Such a history is associated with a longer hospital stay and an increase in morbidity and mortality.[2-4] Among patients who present with seizures related to alcohol use, such as this patient, the risk of death is four times as great as the risk in the general population, although the increased mortality rate seems to be due to the alcoholism itself rather than the seizures.[5]

IDENTIFICATION OF ALCOHOL WITHDRAWAL DELIRIUM

Alcohol withdrawal delirium is a clinical diagnosis and is characterized by the presence of hyperarousal, confusion, hallucinations, hypertension, tachycardia, fever, diaphoresis, and agitated behavior in a patient with an abrupt reduction in alcohol consumption or sudden abstinence from alcohol. Symptoms of withdrawal can differ widely among patients with active alcohol dependence and even among different withdrawal episodes in the same person. A review of this patient's medical record and collateral information from his family indicates past and recent alcohol use, abrupt cessation, and a history of complicated withdrawal. After extubation of the trachea, psychiatric examination of the patient was notable for generalized confusion and encephalopathy; he also reported consistent hip pain and the presence of ecchymosis over his right hip. The family verified that he fell to the right side during his first seizure, which occurred at home.

Although the diagnosis of alcohol withdrawal and related seizures is inescapable in this case, this patient had several risk factors for the development of alcohol withdrawal delirium, the strongest being previous episodes of alcohol withdrawal delirium, seizures related to alcohol withdrawal (past and recent), and possibly concurrent medical issues, including a problem with his hip. Other risk factors in this patient include abrupt cessation of alcohol consumption, a long history of heavy drinking, an age older than 40 years, and an elevated ratio of aspartate aminotransferase to alanine aminotransferase (>1.5:1).

MANAGEMENT OF ALCOHOL WITHDRAWAL DELIRIUM

Once coexisting disorders have been ruled out or adequately addressed, the management of alcohol withdrawal is directed at alleviating symptoms and identifying and correcting metabolic derangements. This patient received aggressive supportive care, including administration of intravenous fluids, nutritional supplementation, and correction of electrolyte deficiencies, along with administration of intravenous thiamine to prevent or treat Wernicke's encephalopathy.

Benzodiazepines are generally considered first-line treatment for alcohol withdrawal syndromes and for the prevention of seizures related to alcohol withdrawal. There is no consensus as to the best benzodiazepine to use; however, long-acting benzodiazepines with active metabolites, such as diazepam, as was used in this case, may allow a smoother course of withdrawal, lower the chance of recurrent seizures, and provide greater efficacy in the prevention of delirium than other benzodiazepines.[6] Benzodiazepines with an intermediate half-life, such as lorazepam, may have a safe profile in patients with hepatic dysfunction.

We elected to treat this patient on the basis of clusters of symptoms. His condition was evaluated with the alcohol withdrawal syndrome "type indicator," a symptom-based assessment tool used to guide treatment decisions and monitor clinical response. The type indicator groups symptoms into categories.[7,8] Type A symptoms are characterized by central nervous system excitation (e.g., anxiety and restlessness) caused by γ-aminobutyric acid (GABA) withdrawal. Type A symptoms are generally treated with GABA agonists, most commonly benzodiazepines. This patient was initially treated with diazepam in a fixed dose, providing coverage for type A symp-

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toms and decreasing the potential for further alcohol withdrawal seizures. Type B symptoms (e.g., fever, diaphoresis, tremor, and elevated blood pressure and heart rate) are caused by adrenergic excess from activation of the locus ceruleus due to a hyperglutamatergic state. Before treating a patient for type B symptoms, other causes of this cluster of symptoms should be ruled out, such as volume depletion, blood loss, and pain. This patient's most notable type B symptom was tachycardia, which was controlled with metoprolol that was also used to treat the underlying atrial fibrillation. Type C symptoms (e.g., confusion, hallucinations, paranoia, and agitation) are caused by excess dopamine release through the mesolimbic tract and are treated with dopamine antagonists. In this patient, we used quetiapine and intravenous haloperidol to target symptoms of hyperarousal, hallucinations, and agitation.

The patient's hospital course was notable for possible neuroleptic malignant syndrome. This rare, life-threatening neurologic disorder is most often caused by an adverse reaction to neuroleptic or antipsychotic drugs. Although a fever developed, as well as variation in blood pressure and increased tone in his arms, the patient did not have the characteristic muscle rigidity or increase in the creatine kinase level often seen in the neuroleptic malignant syndrome. Clinical and physical examinations were notable for ongoing delirium, along with increased paratonia of the arms, which is clinically indicative of extrapyramidal symptoms probably caused by the administration of dopamine antagonists. The treatment for extrapyramidal symptoms is either anticholinergic medications or benzodiazepines, both of which can exacerbate delirium. In a patient with active symptoms of delirium, it is reasonable to attempt to use benzodiazepines before anticholinergic medications, since the likelihood of worsening mental status may be lower with benzodiazepines. We administered three low doses of lorazepam intravenously. Additional doses of intravenous haloperidol administered with lorazepam did not lead to further complications.

MANAGEMENT OF ALCOHOL WITHDRAWAL IN THE ICU

Dr. Ednan K. Bajwa: This patient required admission to an ICU for the management of severe agitation, which is a frequent complication of alcohol withdrawal. The agitation was so extreme that the care providers thought that treatment with propofol, a general anesthetic agent, was warranted. Because a side effect of such treatment is profound depression of consciousness and respiratory drive, the patient required endotracheal intubation and mechanical ventilation.

Patients with symptoms so severe that they require anesthesia and mechanical ventilation are more susceptible to complications during their hospital course. This patient continued to have severe agitation that required continued treatment with high doses of sedative medications, thereby precluding safe extubation and prolonging the need for mechanical ventilation.

Patients in the early stages of alcohol withdrawal may present with initially mild symptoms; aggressive management of the symptoms may prevent progression to severe agitation. Early admission to the ICU can be advantageous because the ICU provides an intensive level of physician and nurse training and staffing, advanced monitoring systems, and the ability to deliver a wide range or high doses — or both — of specific therapies. In this patient, we administered diazepam according to a symptom-triggered escalating-dose strategy.[9] This approach takes advantage of the intensive monitoring that is available in the ICU, including very frequent assessment and dosing of benzodiazepines to control symptoms. Such a strategy can be facilitated by targeting the administration of medication to a threshold of symptoms of alcohol withdrawal. The goal of treatment is to rapidly increase drug doses as needed to achieve the desired level of sedation before severe agitation occurs. The use of diazepam, a medication with multiple active metabolites and therefore a longer duration of action, can help facilitate durable suppression of withdrawal symptoms after initial control of agitation is achieved. This patient had also had multifactorial delirium, which commonly occurs in patients admitted to ICUs, often as part of acute brain dysfunction. As alcohol withdrawal progresses, other causes of delirium may continue to contribute to agitation and complicate the treatment course further. Antipsychotic therapy is commonly used, as in this patient, as an adjunct to benzodiazepines.

In patients in whom treatment with these medications is not adequate, phenobarbital and propofol have both been used successfully to

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treat refractory symptoms. Dexmedetomidine is an α_2-adrenergic agonist that has been approved for use as a sedative in critically ill patients. It has the advantage of alleviating symptoms of agitation while causing less respiratory depression than other agents and therefore can be given without mechanical ventilation. Dexmedetomidine has been used successfully to reduce symptoms of severe agitation in some patients with alcohol withdrawal. Since this regimen has not been well studied, use of this drug should be undertaken with great care.

Dr. Eric S. Rosenberg (Pathology): Dr. Silverman, would you tell us what happened next?

Dr. Silverman: On hospital day 3, the ICU staff attempted to wean the patient from propofol. Each time the propofol dose was lowered, he became increasingly combative, confused, and delirious. We recommended switching to intravenous diazepam while continuing the administration of haloperidol and quetiapine. Within 36 hours after the switch to diazepam, the patient was extubated. Once he was awake, he was somewhat conversant and able to respond to his name and intermittent commands, but he remained delirious. He continued to point to his right hip as a source of pain. An incidental finding on a radiograph of the kidneys, ureter, and bladder (obtained to check for correct nasogastric-tube placement) revealed a fracture of the right proximal femur. The patient was eventually able to be transferred to the hospital medical floor after extubation, although he remained delirious.

Dr. Rosenberg: Dr. Smith, how would you explain this patient's continued delirium?

Dr. Smith: Delirium is a clinical syndrome of many distinct clinical features and causes (Tables 2 and 3).[10,11] There were many factors that probably contributed to the patient's prolonged delirium. He was found to have a fracture of the right proximal femur and underwent placement of a right trochanteric femoral nail on hospital day 7. Both the management of pain from the long-bone fracture with narcotic medications and the postoperative state may have contributed to delirium. Pneumonia and moderate hypoxemia (oxygen saturation, 89 to 90% while the patient was breathing ambient air) also developed. The pneumonia was thought to be caused by multiple microaspiration events, which frequently occur in association with complicated alcohol withdrawal. The patient's history of chronic alcohol dependence put him at risk for the development of Wernicke's encephalopathy, although he received thiamine throughout his hospital stay and did not have ataxia or the ocular findings associated with Wernicke's encephalopathy. Finally, as part of the initial treatment of alcohol withdrawal, the patient received high-dose benzodiazepines. Although the administration of benzodiazepines is the treatment for acute alcohol withdrawal, these medications in clinically significant doses often cause a prolonged confusional state.

Table 2. Clinical Features of Delirium.

Acute onset with fluctuating course
Inattention
Disorganized thinking
Altered level of consciousness
Disorientation
Memory impairment
Perceptual disturbances
Altered psychomotor activity
Disturbance of sleep–wake cycle

Table 3. Common Causes of Delirium.

Metabolic derangements (e.g., hypoglycemia or liver failure)
Infection (e.g., sepsis or pneumonia)
Toxic effects of drug or alcohol use
Withdrawal states (e.g., alcohol or benzodiazepine withdrawal)
Fluid and electrolyte disturbances (e.g., hyponatremia)
Primary brain disorders (e.g., meningitis, stroke, seizure, or Wernicke's encephalopathy)
Low perfusion states (e.g., heart failure or hypoxemia)
Physical disorders (e.g., long-bone fracture)
Postoperative states (especially in the elderly)
Reactions to medications

FOLLOW-UP

Dr. Silverman: After appropriate nutrition and treatment of aspiration pneumonia, the patient's respiratory and mental status gradually improved, and his mental status eventually returned to baseline. He was discharged on hospital day 23. Inpatient medical rehabilitation was recommended,

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which he declined. Seven days after discharge, he presented to the emergency department at this hospital with chills. He said he had been sober from alcohol since discharge and was predominantly focusing on pain issues; he requested pain medication for his hip. He was afebrile, the workup was negative, and he was discharged. Two days later, he was seen by the orthopedics service and his hip incision was noted to be well healed, with intact strength in the right leg. After that, unfortunately, he was lost to follow-up.

Dr. Jerrold F. Rosenbaum (Psychiatry): With the use of diazepam for symptom-triggered treatment, long-acting diazepam metabolites may accumulate and obscure the clinical picture. Would it be beneficial to use shorter-acting agents for patients in the ICU?

Dr. Bajwa: In patients with known liver disease and, therefore, impaired benzodiazepine metabolism, one might choose not to use diazepam. However, for many other patients, the presence of active metabolites may be used to advantage. In patients who are treated with symptom-triggered dosing, we often find an initial rapid escalation of symptoms that requires high doses of diazepam, but only for a short time. The danger lies in causing prolonged sedation with a long-acting drug, but the symptom-triggered approach attempts to avoid this by delivering no more than the minimum amount of medication required for symptom control. Once symptom control has been achieved, dose requirements may decrease rapidly; the recurrence of symptoms may be prevented by the presence of active metabolites, which the patient slowly clears. By contrast, withdrawal symptoms may recur after the use of shorter-acting agents, which are more rapidly cleared.

FINAL DIAGNOSIS

Delirium (alcohol withdrawal delirium and multifactorial delirium).

This case was discussed at Psychiatry Grand Rounds.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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