Persistent altered mental status

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Mr. O, age 24, presents to the ED weak, sluggish, and incoherent. He has a history of schizophrenia and poor medication adherence. What could be causing his persistent altered mental status?

CASE Sluggish, weak, and incoherent

Mr. O, age 24, who has a history of schizophrenia and obesity, presents to the emergency department (ED) for altered mental status (AMS). His mother reports that he has been sluggish, weak, incoherent, had no appetite, and that on the day before admission, he was drinking excessive amounts of water and urinating every 10 minutes.

HISTORY Multiple ineffective antipsychotics

Mr. O was diagnosed with schizophrenia at age 21 and struggled with medication adherence, which resulted in multiple hospitalizations for stabilization. Trials of haloperidol, risperidone, paliperidone palmitate, and valproic acid had been ineffective. At the time of admission, his psychotropic medication regimen is fluphenazine decanoate, 25 mg injection every 2 weeks; clozapine, 50 mg/d; lithium carbonate, 300 mg twice a day; benztropine, 2 mg every night; and trazodone, 50 mg every night.

EVALUATION Fever, tachycardia, and diabetic ketoacidosis

Upon arrival to the ED, Mr. O is obtunded, unable to follow commands, and does not respond to painful stimuli. On physical exam, he has a fever of 38.4°C (reference range 35.1°C to 37.9°C); tachycardia with a heart rate of 142 beats per minute (bpm) (reference range 60 to 100); tachypnea with a respiratory rate of 35 breaths per minute (reference range 12 to 20); a blood pressure of 116/76 mmHg (reference range 90/60 to 130/80); and hypoxemia with an oxygen saturation of 90% on room air (reference range 94% to 100%).

Mr. O is admitted to the hospital and his laboratory workup indicates diabetic ketoacidosis (DKA), with a glucose of 1,700 mg/dL; anion gap of 30 (reference range 4 to 12 mmol/L); pH 7.04 (reference range 7.32 to 7.42); serum bicarbonate 6 (reference range 20 to 24 mEq/L); beta-hydroxybutyrate 11.04 (reference range 0 to 0.27 mmol/L); urine ketones, serum osmolality 407 (reference range 280 to 300 mOsm/kg); and an elevated white blood cell count of 18.4 (reference range 4.5 to 11.0 × 10^9/L). A CT scan of the head is negative for acute pathology.

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Initially, all psychotropic medications are held. On Day 3 of hospitalization, psychiatry is consulted and clozapine, 50 mg/d; lithium, 300 mg/d; and benztropine, 1 mg at night, are restarted; however, fluphenazine decanoate and trazodone are held. The team recommends IV haloperidol, 2 mg as needed for agitation; however, it is never administered.

Imaging rules out deep vein thrombosis, cardiac dysfunction, and stroke, but a CT chest scan is notable for bilateral lung infiltrates, which suggests aspiration pneumonia.

Mr. O is diagnosed with diabetes, complicated by DKA, and is treated in the intensive care unit (ICU). Despite resolution of the DKA, he remains altered with fever and tachycardia.

On Day 6 of hospitalization, Mr. O continues to be tachycardic and obtunded with nuchal rigidity. The team decides to transfer Mr. O to another hospital for a higher level of care and continued workup of his persistent AMS.

Immediately upon arrival at the second hospital, infectious disease and neurology teams are consulted for further evaluation. Mr. O's AMS continues despite no clear signs of infection or other neurologic insults.

At this point, what is the most pressing concern?

a) lung infiltrates
b) nuchal rigidity
c) obtunded mental state
d) persisting tachycardia

The authors' observations

Based on Mr. O's psychiatric history and laboratory results, the first medical team concluded his initial AMS was likely secondary to DKA; however, the AMS continued after the DKA resolved. At the second hospital, Mr. O's treatment team continued to dig for answers.

EVALUATION Exploring the differential diagnosis

At the second hospital, Mr. O is admitted to the ICU with fever (37.8°C), tachycardia (120 bpm), tachypnea, withdrawal from painful stimuli, decreased reflexes, and muscle rigidity, including clenched jaw. The differential diagnoses include meningitis, sepsis from aspiration pneumonia, severe metabolic encephalopathy with prolonged recovery, central pontine myelinolysis, anoxic brain injury, and subclinical seizures.

Empiric vancomycin, 1.75 g every 12 hours; ceftriaxone, 2 g/d; and acyclovir, 900 mg every 8 hours are started for meningoencephalitis, and all psychotropic medications are discontinued. Case reports have documented a relationship between hyperglycemic hyperosmolar syndrome (HHS) and malignant hyperthermia in rare cases[1]; however, HHS is ruled out based on Mr. O's laboratory results. A lumbar puncture and imaging rules out CNS infection. Antibiotic treatment is narrowed to ampicillin-sulbactam due to Mr. O's prior CT chest showing concern for aspiration pneumonia. An MRI of the brain rules out central pontine myelinolysis, acute stroke, and anoxic brain injury, and an EEG shows nonspecific encephalopathy. On Day 10 of hospitalization, a neurologic exam shows flaccid paralysis and bilateral clonus, and Mr. O is mute. On Day 14 of hospitalization, his fever resolves, and his blood cultures are negative. On Day 15 of hospitalization, Mr. O's creatine kinase (CK) level is elevated at 1,308 U/L (reference range 26 to 192 U/L), suggesting rhabdomyolysis.

Given the neurologic exam findings, and the limited evidence of infection, the differential diagnosis for Mr. O's AMS is broadened to include catatonia, neuroleptic malignant syndrome (NMS), serotonin syndrome, and autoimmune encephalitis. The psychiatry team evaluates Mr. O for catatonia. He scores 14 on the Bush-Francis Catatonia Rating Scale, with findings of immobility/stupor, mutism, staring, autonomic instability, and withdrawal indicating the presence of catatonia.[2]

The authors' observations

When Mr. O was transferred to the second hospital, the primary concern was to rule

Clinical Point

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Clinical Point

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Table 1

Diagnostic criteria for neuroleptic malignant syndrome

Feature	Description
Exposure to a dopamine antagonist	First- or second-generation antipsychotic use
Hyperthermia	>100.4°F or >38.0°C on at least 2 occasions
Rigidity	Rigidity is usually of the "lead-pipe rigidity" type
Altered mental status	Hyperactive or hypoactive delirium
Serum creatine kinase elevation	At least 4 times the upper limit of normal
Sympathetic nervous system lability	Blood pressure elevation, ≥25% above baseline Blood pressure fluctuation, ≥20 mmHg (diastolic) or ≥25 mmHg (systolic) changes within 24 hours Tachycardia, ≥25% above baseline Tachypnea, ≥50% above baseline
Negative workup for other etiologies	—
"Atypical" or early neuroleptic malignant syndrome	
Rigidity may be milder or absent Fever might be absent Any 2 of the symptoms list above in the setting of an offending agent, and other medical causes of the symptoms have been ruled out	

Source: References 3,4

out meningitis due to his unstable vitals, obtunded mental state, and nuchal rigidity. A comprehensive infectious workup, including lumbar puncture, was imperative because infection can not only lead to AMS, but also precipitate episodes of DKA. Mr. O's persistently abnormal vital signs indicated an underlying process may have been missed by focusing on treating DKA.

TREATMENT Finally, the diagnosis is established

A lorazepam challenge is performed, and Mr. O receives 4 mg of lorazepam over 24 hours with little change in his catatonia symptoms. Given his persistent fever, tachycardia, and an elevated CK levels in the context of recent exposure to antipsychotic medications, Mr. O is diagnosed with NMS (***Table 1***[3,4]) and is started on bromocriptine, 5 mg 3 times daily.

What is the mechanism of action of bromocriptine?

a) *N*-methyl-D-aspartate (NMDA) receptor antagonist
b) positive allosteric modulator of GABA-A receptor
c) postsynaptic dopamine D2 receptor agonist
d) skeletal muscle relaxant

The authors' observations

Mr. O's complicated medical state—starting with DKA, halting the use of antipsychotic medications, and the suspicion of catatonia due to his history of schizophrenia—all distracted from the ultimate diagnosis of NMS as the cause of his enduring AMS and autonomic instability. Catatonia and NMS have overlapping symptomatology, including rigidity, autonomic instability, and stupor, which make the diagnosis of either condition complicated. A positive lorazepam test to diagnose catatonia is defined as a marked reduction in catatonia symptoms (typically a 50% reduction) as measured on a standardized rating scale.[5] However, a negative lorazepam challenge does not definitely rule out catatonia because some cases are resistant to benzodiazepines.[6]

Table 2

Pharmacologic treatment of neuroleptic malignant syndrome

Medication and dosage	Mechanism of action	Notes
Lorazepam, 1 to 2 mg IM or IV every 4 to 6 hours Diazepam, 10 mg IV every 8 hours	Positive allosteric modulator of GABA-A receptor	Mild to moderate cases Administer with or without bromocriptine or amantadine
Bromocriptine, 2.5 to 5 mg by mouth every 8 hours	Postsynaptic dopamine D2 receptor agonist	Moderate to severe cases Counteract D2 blockade of antipsychotics Administration should be by mouth and can be via feeding tube
Amantadine, 100 mg by mouth every 8 hours	Nonspecific: Direct increase of dopamine release, reduce dopamine reuptake, anticholinergic, weak NMDA receptor antagonist	Moderate to severe cases
Dantrolene, 1 to 2.5 mg/kg IV every 6 hours	Blocks calcium efflux from sarcoplasmic reticulum to directly relax skeletal muscle	Most severe cases

NMDA: N-methyl-D-aspartate

Source: References 3,11,12

NMS risk factors relevant in this case include male sex, young age, acute medical illness, dehydration, and exposure to multiple psychotropic medications, including 2 antipsychotics, clozapine and fluphenazine.[7] DKA is especially pertinent due to its acute onset and cause of significant dehydration. NMS can occur at any point of antipsychotic exposure, although the risk is highest during the initial weeks of treatment and during dosage changes. Unfortunately, Mr. O's treatment team was unable to determine whether his medication had been recently changed, so it is not known what role this may have played in the development of NMS. Although first-generation antipsychotics are considered more likely to cause NMS, second-generation antipsychotics (SGAs) dominate the treatment of schizophrenia and bipolar disorder, and these medications also can cause NMS.[8] As occurred in this case, long-acting injectable antipsychotics can be easily forgotten when not administered in the hospital, and their presence in the body persists for weeks. For example, the half-life of fluphenazine decanoate is approximately 10 days, and the half-life of haloperidol decanoate is 21 days.[9]

OUTCOME Improvement with bromocriptine

After 4 days of bromocriptine, 5 mg 3 times daily, Mr. O is more alert, able to say "hello," and can follow 1-step commands. By Day 26 of hospitalization, his CK levels decrease to 296 U/L, his CSF autoimmune panel is negative, and he is able to participate in physical therapy. After failing multiple swallow tests, Mr. O requires a percutaneous endoscopic gastrostomy (PEG) tube. He is discharged from the hospital to a long-term acute care facility with the plan to taper bromocriptine and restart a psychotropic regimen with his outpatient psychiatrist. At the time of discharge, he is able to sit at the edge of the bed independently, state his name, and respond to questions with multiple-word answers.

Which medication can most safely be used in the future to treat Mr. O's schizophrenia?

a) aripiprazole extended-release injectable suspension

continued

Clinical Point

Catatonia and NMS have overlapping symptomatology, which make the diagnosis of either condition complicated

b) clozapine
c) chlorpromazine
d) quetiapine

The authors' observations

The most common pharmacologic treatments for NMS are dantrolene, bromocriptine, benzodiazepines (lorazepam or diazepam), and amantadine.[3] Mild cases of NMS should be treated with discontinuation of all antipsychotics, supportive care, and benzodiazepines.[3] Bromocriptine or amantadine are more appropriate for moderate cases and dantrolene for severe cases of NMS.[3] All antipsychotics should be discontinued while a patient is experiencing an episode of NMS; however, once the NMS has resolved, clinicians must thoroughly evaluate the risks and benefits of restarting antipsychotic medication. After a patient has experienced an episode of NMS, clinicians generally should avoid prescribing the agent(s) that caused NMS and long-acting injections, and slowly titrate a low-potency SGA such as quetiapine.[10] ***Table 2***[3,11,12] (***page 49***) outlines the pharmacologic treatment of NMS.

Clinical Point

The most common pharmacologic treatments for NMS are dantrolene, bromocriptine, benzodiazepines, and amantadine

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Related Resource

- Turner AH, Kim JJ, McCarron RM. Differentiating serotonin syndrome and neuroleptic malignant syndrome. Current Psychiatry. 2019;18(2):30-36.

Drug Brand Names

Acyclovir • Zovirax
Amantadine • Gocovri
Ampicillin-sulbactam • Unasyn
Aripiprazole • Abilify Maintena
Benztropine • Cogentin
Bromocriptine • Cycloset, Parlodel
Ceftriaxone • Rocephin
Clozapine • Clozaril
Dantrolene • Dantrium
Diazepam • Valium
Haloperidol • Haldol
Lithium • Eskalith, Lithobid
Lorazepam • Ativan
Paliperidone palmitate • Invega Sustenna
Quetiapine • Seroquel
Risperidone • Risperdal
Valproate sodium • Depakote
Trazodone • Oleptro
Vancomycin • Vancocin

Bottom Line

Neuroleptic malignant syndrome (NMS) should always be part of the differential diagnosis in patients with mental illness and altered mental status. The risk of NMS is especially high in patients with acute medical illness and exposure to antipsychotic medications.