Broad Differential Diagnoses in a Case of Catatonia Secondary to Clozapine Withdrawal

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Catatonia is a complex neuropsychiatric syndrome characterized by motor, behavioral, and affective symptoms.[1] The pathophysiology of catatonia remains unclear, although dysregulation in the activity of dopamine, glutamate, and γ-aminobutyric acid (GABA) has been implicated.[1] While catatonia may arise in the context of various medical provocations, including psychiatric, neurological, toxicological, and immunological etiologies, it has also been observed to occur with clozapine discontinuation.[2,3] The hypothesized mechanism of clozapine withdrawal catatonia involves clozapine's purported ability to increase GABA activity in certain areas of the brain through direct and indirect effects on GABAergic interneurons.[4] Clozapine withdrawal catatonia typically shows a limited response to initiating benzodiazepines but a robust response to reintroducing clozapine.[4,5] This case report underscores the critical need to identify and manage clozapine withdrawal catatonia by promptly restarting clozapine when benzodiazepines are ineffective.

Case Report

A 56-year-old woman with a history of schizophrenia on an outpatient regimen of intramuscular (IM) haloperidol decanoate 150 mg monthly (last administered 2 weeks before admission), valproic acid 1,250 mg orally daily, and clozapine 200 mg orally at bedtime presented to the emergency department (ED) with resting tremors in the extremities. Collateral reported the patient had discontinued clozapine, believing it to be the cause of her tremors.

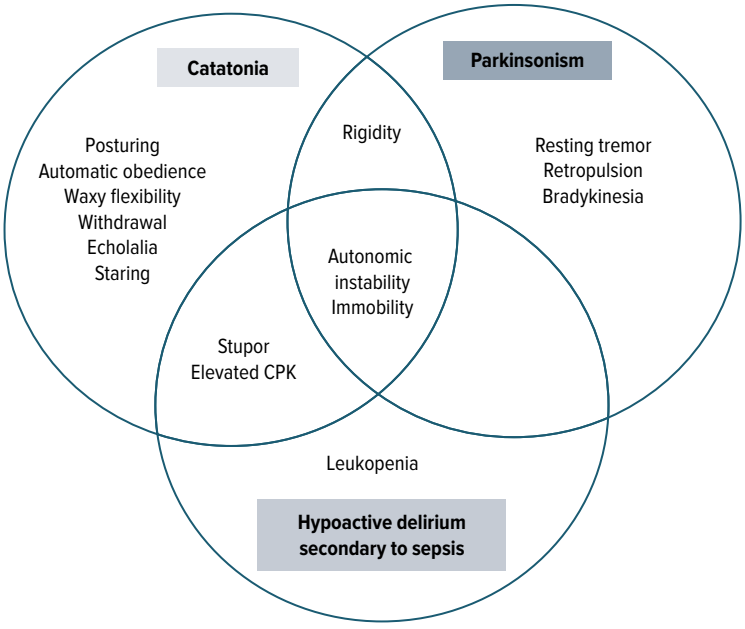
In the ED, the patient was noted to be staring, hypoactive, and rigid, with a Bush-Francis Catatonia Rating Scale (BFCRS)[6] score of 13. She showed no improvement after 2 doses of IM lorazepam 2 mg, but her tremors improved after IM benztropine 2 mg. She was started on intravenous (IV) lorazepam 2 mg twice/day (BID) for catatonia and IV benztropine 1 mg BID for parkinsonian symptoms of unclear etiology, including retropulsion and bradykinesia. She was then admitted to the medicine department.

From admission day 1 to day 4, her catatonia symptoms worsened to a BFCRS score of 17. Laboratory tests revealed elevated ammonia (72 µmol/L), serum valproic acid level (109.9 µg/mL), and creatine phosphokinase (643 U/L). Urinalysis showed positive leukocyte esterase. Other workup, including head computed tomography, brain magnetic resonance imaging, lumbar puncture, and electroencephalography, revealed no etiology for the catatonia.

Due to hyperammonemia, valproic acid was discontinued. Ceftriaxone was started to treat a urinary tract infection (UTI). Lorazepam was gradually titrated to 3 mg IV 4 times per day, but the patient's catatonia symptoms did not improve, and she appeared oversedated.

From admission day 5 to day 7, the patient showed no significant response to lorazepam and instead exhibited worsening immobility and

Figure 1.
Symptom Overlap Complicating the Diagnosis of Catatonia



Abbreviation: CPK = creatine phosphokinase.

withdrawal, eventually necessitating nasogastric tube placement. Additionally, the patient developed a febrile episode to 101.3°F, decreased urine output, and intermittent tachycardia despite treatment of the UTI with ceftriaxone, raising concern for the development of malignant catatonia. Benztropine was discontinued due to concern of anticholinergic side effects.

Given the lack of response to lorazepam, clozapine was reintroduced at 25 mg at bedtime on admission day 7 once the nasogastric tube was placed and increased by 25 mg every 2 days. Four days after clozapine was reintroduced, she began to show improvements in voluntary movements. As clozapine was increased, lorazepam was slowly tapered and discontinued. By admission day 19, her catatonia completely resolved, and her vitals stabilized.

Discussion

This case presents a complex clinical scenario in which no single diagnosis fully accounted for the presenting symptoms. Plausible differential diagnoses included delirium, idiopathic Parkinson disease, medication-induced parkinsonism, neuroleptic malignant syndrome, stroke, and seizures. Figure 1 depicts the symptom overlap of catatonia, parkinsonism, and hypoactive delirium secondary to sepsis. In such complex cases, it may be necessary to simultaneously address multiple competing differential diagnoses before they can be definitively ruled out. This case highlights the potential benefit of clozapine when malignant catatonia is among the differential diagnoses. Reinitiation of clozapine should be considered when clozapine withdrawal is a suspected etiology of catatonia, as benzodiazepines alone may not be sufficient.[4]

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