Sudden-Onset Catatonia Following Clozapine Withdrawal: A Case Report

To the Editor: Sudden discontinuation of clozapine is frequently required in clinical practice, particularly in cases of blood dyscrasia or suspected myocarditis. Abrupt discontinuation of clozapine is known to carry the risk of rebound psychosis[1–3] but also acute physical deterioration including delirium,[4] vomiting,[5] dyskinesias,[6] and catatonia.[7–11] We report the case of Mr A, a patient who became catatonic 4 days after clozapine cessation.

Case report. The 22-year-old patient's psychotic illness dated to June 2011, when he responded initially to olanzapine but deteriorated within 6 months. Further trials of olanzapine and quetiapine had been unsuccessful. Two trials of clozapine in 2013 were stopped after a month each (suspicion of pericarditis and a finding of eosinophilia).

Clozapine treatment was restarted in February 2015 with cardiology monitoring (twice-weekly troponin and C-reactive protein [CRP] tests; echocardiography at baseline and 6 weeks). At the fifth week (clozapine titrated over 4 weeks to 150 mg twice per day; level = 0.22 mg/L), troponin and CRP became marginally elevated, and the patient was transferred to an emergency department, where pericarditis and myocarditis were excluded. Upon Mr A's return to the psychiatric ward, clozapine was switched to risperidone pending cardiology advice.

Four days later, Mr A developed malaise, tachycardia, drowsiness, and agitation. His inflammatory markers were raised (white blood cell count of 13.2×10^9/L and CRP of 85 mg/dL), but clinical examination, chest x-ray, urine test, and electrocardiogram results were normal.

The patient's inflammatory markers improved with empirical antibiotic treatment. However, Mr A became less fluent and developed stiffness, coarse Parkinsonian tremor, and increased reflexes bilaterally with 4 beats of clonus. His creatine kinase (CK) level was 599 IU/L initially, rising to 2,205 IU/L and then 1,486 IU/L on the third and fourth days, respectively.

Clozapine withdrawal was suspected given unremarkable neurologic investigations (computed tomography of the head, lumbar puncture, autoantibody screen, and electroencephalogram), leading to a change from risperidone (0.5 mg twice per day) to oral lorazepam 0.5 mg four times per day with good effect (improvement in rigidity 45 minutes after first administration). Oral dantrolene 25 mg once daily was also started in view of potential neuroleptic malignant syndrome (NMS). The patient recovered on the seventh day of the admission, and dantrolene treatment was stopped when his CK level came down to 473 IU/L.

The patient was uneventfully retitrated on clozapine at 12.5-mg daily increments, and 9 months later he remains well on a stable 450-mg daily dose (clozapine level = 0.35 mg/L). Collateral history revealed a similar episode of stupor, rigidity, and mutism several days after abrupt clozapine cessation in May 2013.

The presentation, benzodiazepine response, and history of a similar reaction to clozapine withdrawal favor clozapine cessation–induced catatonia. In a similar case, a patient suffered 2 identical catatonic presentations 2 years apart, both shortly after sudden clozapine cessation.[10] In another report, mutism, posturing, waxy flexibility, and no spontaneous oral intake developed 2 days after clozapine was stopped.[11] Similarly, the symptoms resolved with lorazepam and electroconvulsive therapy.

NMS remains a significant differential. A clear-cut distinction, however, may not be neurobiologically valid, as illustrated by another clozapine withdrawal in which catatonia transformed into NMS following antipsychotic treatment.[7] This suggests that NMS may be a neuroleptic-induced subtype of catatonia.

Clozapine withdrawal reactions may be due to muscarinic (presenting with nausea, vomiting,[5] and delirium[4]) or dopaminergic (dystonias and dyskinesias,[6] catatonia) rebound. Anticholinergics and olanzapine have been proposed as treatment options for preventing withdrawal when clozapine is discontinued acutely.[12,13]

Acute physical deterioration is an infrequent but severe complication of sudden clozapine discontinuation. The presentation could be predominantly dopaminergic in origin with catatonic features or cholinergic with nausea/vomiting or delirium. Awareness of clozapine withdrawal reactions is important for the recognition and management of these syndromes. Clozapine can safely be reinstated following withdrawal reactions.

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