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LETTER TO THE EDITOR

Recurrent catatonia: Secondary to infection and sudden discontinuation of clozapine

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Dear Editor,

Catatonia can occur in psychotic and mood disorders and may also be secondary to numerous non-psychiatric causes (1). Clozapine is the gold standard treatment for treatment-resistant schizophrenia (2). However, abrupt discontinuation of clozapine—whether uncontrolled by a physician or necessitated by life-threatening side effects—can lead to various adverse outcomes, including psychotic symptoms, serotonergic and cholinergic symptoms, and catatonia (3). Here, we present the case of a 48-year-old female patient who developed recurrent catatonia, initially triggered by clozapine withdrawal and later exacerbated by a urinary tract infection.

The patient was admitted to our clinic with complaints of immobility, refusal to eat and drink, and sudden episodes of aggression. She had been receiving clozapine treatment for 30 years following a diagnosis of schizophrenia, with two prior discontinuations resulting in catatonic symptoms—once 28 years ago due to pregnancy and again 18 years ago without medical advice. Both episodes of catatonia responded well to electroconvulsive therapy (ECT) and the resumption of clozapine treatment. It was reported that the patient abruptly discontinued her 500 mg/day clozapine treatment two weeks prior. Insomnia, aggression, and self-talking began on the seventh day of withdrawal. On the same day, treatment with olanzapine 20 mg/day and a 100 mg/month paliperidone palmitate long-acting injection was initiated at another psychiatry outpatient clinic. On the 12th day, the patient ceased eating, speaking, and moving, and on the 13th day, she remained motionless for an extended period before attempting to jump from a height following a sudden increase in movement. Fourteen days after clozapine withdrawal, the patient was admitted to our inpatient clinic with mutism, negativism, and grimacing. Posturing and agitation observed during the examination confirmed five DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria for catatonia, exceeding the minimum requirement of three. The Bush-Francis Catatonia Rating Scale score was 16. Laboratory tests and a brain computed tomography (CT) scans revealed no organic pathology or significant abnormalities.

The treatment plan initially included clozapine and lorazepam; however, due to the patient's non-compliance with oral intake, her high risk of agitation, and the deterioration of her general medical condition, electroconvulsive therapy was initiated on the second day of hospitalization. After the second ECT session, the patient's mutism, immobility, and refusal to eat resolved. The ECT course was completed after 10 sessions. Once the psychotic symptoms and catatonic state

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subsided, the patient was discharged on the 37th day of hospitalization with a treatment regimen of clozapine 500 mg/day, amisulpride 600 mg/day, and biperiden 2 mg/day.

The patient was readmitted three weeks after the initial discharge due to paranoid and obsessive thoughts. Fluoxetine 20 mg/day and lorazepam 2.5 mg/day were added to her treatment regimen. On the eighth day of hospitalization, posturing, negativism, refusal to eat and drink, and grimacing were unexpectedly observed. The Bush-Francis Catatonia Rating Scale score was determined to be 7. There were no fluctuations in consciousness or signs of disorientation. Blood tests revealed no abnormalities, but a urine dipstick test showed leukocyte (3+) and erythrocyte (1+) positivity. Based on the interdisciplinary recommendation of an infectious disease and clinical microbiology specialist, ciprofloxacin 1500 mg/day was added to her treatment, while the psychiatric regimen remained unchanged. The catatonia symptoms resolved on the third day after initiating antimicrobial therapy, and a follow-up urine dipstick test showed no pathological findings. Monthly observations over the three months following discharge indicated no recurrence of catatonia or psychotic exacerbation. The patient's obsessive symptoms showed partial improvement with the treatment. She continued follow-up care at the psychiatric outpatient clinic in her city and actively participated in a teleconference with her family five months post-discharge. It was confirmed that she adhered to her medication regimen and experienced no relapse of catatonia or exacerbation of psychotic symptoms. Informed consent for this report was obtained from the patient and her next of kin, her son, who also served as her caregiver.

Studies indicate that catatonia is associated with a general medical condition in approximately 20% of cases (4). A reported case demonstrated catatonia due to infection resolving with antibiotherapy, without the use of high-dose benzodiazepine or ECT, similar to the findings in our case (5). In this case, there was a strong correlation between the recurrence of catatonia symptoms and signs of infection. Psychiatric treatment remained unchanged, and catatonia symptoms improved dramatically with the addition of antimicrobial therapy. Repeated urinary infection tests further supported this improvement. Similarly, studies investigating the relationship between catatonia and the immune system highlight the hypofunction of the glutamatergic system (6). Recent research indicates that the gamma-aminobutyric acid (GABA)-ergic system is expressed not only in neurons but also in immune cells such as lymphocytes. As a result, it may represent a new therapeutic target for inflammatory and autoimmune diseases. A literature review by Rogers et al. (4) emphasized the close relationship between anti-NMDAR (anti-N-methyl-D-aspartate receptor) encephalitis and catatonia. This highlights the role of the GABAergic system in the pathophysiology of catatonia and in the mechanism of action of clozapine.

Clozapine is the only antipsychotic that induces catatonia following its withdrawal (7). Various theories have been proposed regarding the mechanism of catatonia after clozapine withdrawal. Studies suggest that it may result from cholinergic and serotonergic rebound-related hyperactivity and increased dopamine receptor activity (8). Lander et al. (7) examined 55 cases of catatonia, 24 of which developed after benzodiazepine withdrawal and 20 after clozapine withdrawal. They identified GABA receptors as a shared pharmacological mechanism. Another perspective, based on studies of clozapine's effects on GABA receptor activity, suggests that decreased GABAa receptor activity and increased GABAb receptor activity may contribute to post-withdrawal catatonia. The fluctuating nature of catatonia symptoms further supports this hypothesis (9). Clozapine continues to be significant both for its potential to induce catatonia when abruptly discontinued and for its efficacy in treatment. This could provide insight into the mechanism of action of clozapine and the pathophysiology of catatonia.

In summary, two distinct causes of catatonia were observed in this case. It is noteworthy that both point to the GABAergic system as a key factor. Clarifying the role of GABA receptors in catatonia may also help elucidate the mechanisms of action of clozapine and ECT.

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