Olanzapine-Induced Malignant Neuroleptic Syndrome

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Neuroleptic malignant syndrome (NMS), caused by antipsychotic therapy, shows itself with mental status alteration, high fever, autonomic dysfunction, and muscle rigidity. It is a rare idiosyncratic reaction with mortality risk. The etiology is still unknown. NMS-related mortality and morbidity can be decreased by cessation of the used drug and aggressive treatment. Olanzapine is a thienobenzodiazepine, a member of atypical antipsychotic drugs; its structure and effects on neurotransmitters resemble clozapine. Here we report a case of bipolar disorder receiving olanzapine therapy for 10 years, who developed NMS without rigidity. We emphasized the importance of early hydration and hemodiafiltration therapy.

Key Words: Neuroleptic malignant syndrome, olanzapine, rigidity, hemodiafiltration

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, but potentially life threatening idiosyncratic reaction mostly associated with antipsychotic drugs. The syndrome is initiated by the addition of a new drug to pre-existing treatment or by increasing the dosage of the used drug. Clinical findings include fever, tachycardia, muscular rigidity (lead-pipe type) and increased muscle tone, altered mental status, leucocytosis and increased serum creatinine phosphokinase (CPK) levels (1). NMS should be suspected in case there is autonomic instability, neuromuscular or central nervous system dysfunction in patients.

Olanzapine is a thienobenzodiazepine class atypical antipsychotic drug that has a similar effect on neurotransmitters as clozapine and effective on serotonin (5HT_{2a/2c}), dopamine (D₁₋₄), muscarinic (M₁₋₆) histamine (H₁) and adrenergic α -1 receptors. Different from classical antipsychotics, although its antagonistic effect on dopamine receptors is lower, it has an antagonistic effect against serotonin receptors. It is increasingly used in the treatment of psychosis with its lower incidence of side effects compared to classical neuroleptics. In this case report, an Olanzapine-related NMS case without muscle rigidity is presented.

Case Presentation

A 42-years old, married, primary school graduate female patient was brought to the emergency department as she could not be awakened from sleep for 24 hours. She was receiving Olanzapine treatment (10 mg/days) for bipolar disorder for 5 years. The patient had loss of appetite, fatigue, dysphagia, restlessness, changes in consciousness and mood disorder for the last 10 days. She had no response to verbal and painful stimuli, her body temperature was 38.4°C, she had tachycardia (pulse rate>140/min), hypotension (non-invasive blood pressure=70/40 mmHg) and decreased oxygen saturation (SpO₂ 85%). As her breathing pattern worsened, she was intubated and hospitalized in the reanimation unit for advanced medical investigation and treatment. Mechanical ventilation was initiated and the patient was administered fluid and midazolam infusion for sedation.

Her chest X-ray was normal. Electrocardiographic findings were consistent with subacute antero-posterior myocardial infarction. Laboratory values were as follows, creatinine 2.5 mg dL⁻¹ (0.72-1.25 mg dL⁻¹), CPK 4560 U L⁻¹, Troponin I 18.90 ng dL⁻¹ (0-0.4 ng mL⁻¹), and CK-MB 12.5 ng dL⁻¹ (0.6-6.3 ng mL⁻¹). Complete blood count revealed mild leucocytosis (10.6 10³ U L⁻¹). Differential diagnosis included sinus vein thrombosis, intracranial bleeding, intoxication, infection, serotonergic

syndrome and intracranial mass lesion. As there was no history and clinical findings of intoxication, no laboratory and clinical findings consistent with infection, no metabolic condition or drug that may increase the levels of serotonin and as cranial CT and MRI revealed no mass lesion, bleeding, and sinus vein thrombosis, these conditions were excluded. Cranial MRI revealed a subacute infarction in the parietal cortex. Although the patient did not have muscular rigidity NMS diagnosis was made considering that although rare, NMS may be caused by atypical neuroleptics, and bromocriptine was added to the treatment.

Blood pressure and body temperature was monitored and daily fluid-electrolyte balance, renal and hepatic function tests, blood gas values, CPK, Troponin I, CK-MB and CBC were followed up. Creatinine values increased to 5.06 mg dL⁻¹, Troponin I to 96.4 ng mL⁻¹ and CK-MB to 44.4 ng mL⁻¹. At the 3rd day of hospitalization, when CPK levels increased to 42.123 U L⁻¹ and urine output decreased to 50 mL hours⁻¹, haemodiafiltration treatment was initiated and at the end of two days CPK levels decreased to 55 U L⁻¹ and creatinine levels returned to normal. For the treatment of fever, external cooling and intravenous paracetamol was given, when necessary. Although there was improvement in the general condition of the patient, she did not recover consciousness and could not be separated from the mechanical ventilator; therefore percutaneous tracheostomy was performed at 12 days of intubation. In the following days, consciousness and respiratory effort of the patient improved day-by-day and the patient was weaned from the ventilator at 20 days, her tracheostomy was closed at 30 days and she was discharged from the hospital at 35 days. On discharge, the patient was conscious, cooperated and oriented. Motor examination revealed 4/5 strength in all four extremities. She was able to walk with assistance. Her sensory examination findings were normal and deep tendon reflexes were normoactive without any pathologic reflexes. The patient who was not able to recall the disease period had a depressive mood and displayed a blunted affection. A control appointment was scheduled 1 month later and the patient was discharged after consent was obtained from her and her family. Muscular rigidity was not seen in the follow-up period of 35 days.

In the follow-up after discharge, it was learned that she was not able to take care of herself as previously and required her family's care; she was sluggish and became introverted. Additionally, she had amnesia for her disease. The patient, who was re-evaluated by the Psychiatry department 1 month later, was started on sertraline treatment.

Discussion

Neuroleptic malignant syndrome was first defined by Delay and Deniker, as a clinical condition caused by antipsychotic drugs or other drugs affecting dopamine levels (2, 3).

According to DSM-IV-TR, the diagnosis of neuroleptic malignant syndrome can be made by the presence of at least two or more findings including rise in body temperature and rigidity (major findings), sweating, palpitation, altered or generally elevated blood pressure, high leucocyte counts, altered mental status, tremor, urinary or faecal incontinence and CPK elevation (minor findings) (4).

Compared to atypical antipsychotic drugs, neuroleptic malignant syndrome more frequently develops due to the use of typical antipsychotic drugs. Although rarely encountered, it is a condition that requires emergency treatment as it can be life-threatening (5).

Neuroleptic malignant syndrome is suggested to develop idiosyncratically. Its cause is still unknown. At the centre of all available theories there is dopamine receptor blockade (1). Its incidence has been reported to be 0.07%-0.9% in patients treated chronically with neuroleptic agents (6, 7). Additionally, several publications report that its prevalence has risen to 3% and it is more frequently encountered in young males (8, 9).

Mortality is due to systemic complications and autonomic dysfunction. Mortality rates decreased to 4%-30% by early diagnosis and effective treatment methods and increase in awareness of the syndrome (10). Although NMS generally occurs due to typical neuroleptics, it may develop due to atypical antipsychotics with lower efficacy and even with antiemetic drugs such as metoclopramide and promethazine (11, 12). It generally occurs in the first 2 weeks of treatment but may even develop after taking a single dose or similar to the present case, may develop in patients using the same dose for years (13). Our patient was using Olanzapine at a dose of 10 mg day⁻¹ for 5 years and has not previously experienced such a condition.

However, milder or atypical NMS cases have also been reported in the literature. These are cases that develop due to the use of agents with lower efficacy like atypical neuroleptics, or cases with early diagnosis. Rigidity may be milder or absent, as was in the present case (14). Cases without fever have also been reported (15).

CPK levels are typically above 1000 IU L⁻¹ in patients with neuroleptic malignant syndrome and even may increase to 100.000 IU L⁻¹. The level of CPK elevation is correlated with disease severity (16). CPK levels increased to 42.000 IU L⁻¹ in our patient, and on detecting high creatinine levels and decreased urine output, haemodiafiltration treatment was initiated without waiting for further increase in CPK levels.

The other frequent, but non-specific laboratory findings of neuroleptic malignant syndrome are as follows, leucocytosis, mild elevation in lactate dehydrogenase, transaminase and alkaline phosphatase levels, electrolyte disturbances, acute renal

failure due to myoglobinuria, and decreased serum iron concentrations (17). Electrolyte disturbances and acute renal failure developed in the follow-up period of the present case was easily treated with haemodiafiltration treatment in a short period.

Cardiac arrhythmias, myocardial infarction, cardiomyopathy, respiratory insufficiency, deep vein thrombosis, thrombocytopenia, disseminated intravascular coagulation, liver failure, renal failure and sepsis may also develop in the follow-up of neuroleptic malignant syndrome. Therefore, the patients should be followed up in intensive care units with all sorts of facilities, under monitoring for 24 hours.

Besides supportive therapy, dantrolene, amantadine, bromocriptine, benzodiazepines and electroconvulsive therapy can also be used in the treatment of neuroleptic malignant syndrome. Bromocriptine is a dopamine agonist, and is used for restoring dopaminergic tone. It is recommended to be used for 10 days after NMS is taken under control and then discontinued. We also used bromocriptine (nasogastric 2.5 mg 4X1) in the present case, as recommended.

Most of the cases recover in two weeks. Our patient also showed clinical recovery in approximately 3 weeks. The rate of permanent sequelae after NMS is reported to be between 3.3% and 10% (18). The most frequent sequelae are joint contractures, mild cognitive loss, tremor and extrapyramidal system findings (19). Approximately 4-30% of the patients die (10). Causes of death are respiratory insufficiency, cardiac arrest or renal failure due to muscle breakdown (20). However, by initiating hemodiafiltration therapy, we treated these complications, which increase mortality in the early period. There was no improvement in the cognitive and memory loss of the patient in 6 months follow-up period.

Conclusion

Conclusively, NMS is a rare, but life-threatening neuropsychiatric emergency. Early diagnosis and treatment is substantially important in decreasing mortality and morbidity. Absence of important findings such as fever or rigidity in a patient suspected of NMS does not rule out the diagnosis. When NMS is suspected, the drug used should be discontinued and the patient should be followed-up in intensive care unit under monitoring. We suggest that, among supportive therapies, fluid treatment and early haemodiafiltration is beneficial in the treatment of this condition.

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