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Case Report

Complementary/Alternative Medicine Section

Delayed Diagnosis of Atypical Neuroleptic Malignant Syndrome Precipitated by Olanzapine: A Case Report

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is a life-threatening and idiosyncratic adverse reaction to common antipsychotic medication. The diagnosis of NMS remains controversial and unclear, as most criteria used in practice fail to correspond to empirical diagnoses. Here, we present a case of NMS diagnosis and management. A 48-year-old man with bipolar disorder was frequently admitted to a psychiatric ward with recurrent episodes. He had been stable for six months since his last hospitalisation and was being treated with oxcarbazepine and olanzapine. Oxcarbazepine was discontinued, and olanzapine (20 mg/d) was continued because of hyponatraemia and hypochloraemia. Clinical manifestations after olanzapine intake comprised confusion, agitation, fever, urinary retention, and increased Creatine Kinase (CK). A urinary tract infection was considered because of absent muscle rigidity in the first five days. Furthermore, the patient had an increased body temperature, frequent urination, urgency, and pain. Upon muscle rigidity and pulmonary infection development, the patient was medically treated. Following quetiapine monotherapy (administered at 25 mg and gradually increased to 600 mg in two oral doses) at week 3 post-NMS recovery, the mental state of the patient improved. He maintained a rational conversation with no evidence of autonomic instability or disorientation. He was discharged from the psychiatric ward 3.5 months after admission. NMS is a rare neurological disorder with a potential atypical presentation and requires emergency medical treatment rather than psychiatric care. Clinicians must carefully distinguish between medical and mental illnesses, prioritising multiple illnesses promptly in case of identification difficulties.

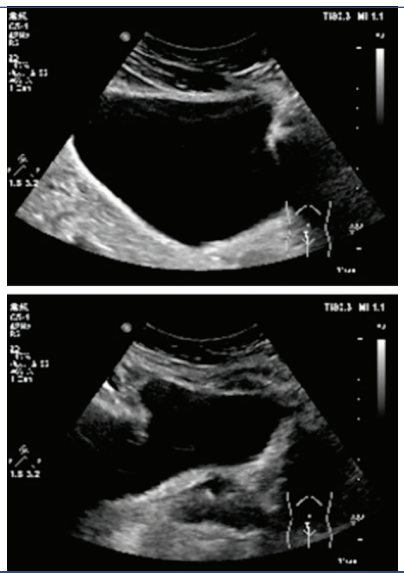
Keywords: Adverse drug reaction, Hypochloraemia, Hyponatraemia, Serotonin syndrome

CASE REPORT

A 48-year-old male with frequent episodes of bipolar disorder over a span of 26 years was admitted to a psychiatry department upon experiencing recurrent excitement without titrating olanzapine, talkativeness, and temper tantrums for two weeks. The patient remained stable for six months on oxcarbazepine (1.8 mg/day) and olanzapine (20 mg/day). Oxcarbazepine was discontinued because of hyponatraemia and hypochloraemia (serum sodium and chlorine: 105.3 and 69.1 mmol/L, respectively) until the seventh month. The patient practiced healthy life habits, had no relevant family history, and was in good health.

On day 3, he became delirious and exhibited unusual behaviours, including reticence or mutism, playing with water in the toilet, wetting his clothes, and demonstrating urination difficulties. On day 5, the patient exhibited muscular stiffness similar to catatonia. The olanzapine dose was reduced to 10 mg/day, and a psychiatrist prescribed lorazepam 1 mg (temporarily) for hypertonia. The on-call medical team was contacted for assistance. The patient had a body temperature of >38°C and experienced frequent, urgent, and painful urination. Microscopy examinations (+/high-power lens) revealed that the urine contained white blood cells. Colour ultrasound images revealed an enlarged prostate with a calcification focus, suggesting urinary tract infection [Table/Fig-1]. On day 11, the patient experienced expectoration difficulties. Hence, olanzapine was discontinued. The medical team considered a provisional diagnosis of pneumonia and malignant syndrome, and the patient was thus transferred to a medical ward.

Head magnetic resonance imaging revealed no abnormalities. On day 3, although the patient developed low-grade fever (37.5°C), all other vital signs were normal. Laboratory results indicated 139.1 mmol/L serum sodium, 106.7 mmol/L serum chlorine, 284 U/L CK, and 7.8 mmol/L urea nitrogen. On day 5, the patient displayed a moderate fever (38.9°C), rapid pulse and respiration (110 and 25/min, respectively), increased blood pressure (156/96 mmHg), significantly increased muscle tone, and negative neuropathologic signs. On average, the leukocyte count (19.9×10^9/L), hypersensitive C-Reactive Protein (59.2 mg/L), and CK (3630 U/L) were significantly increased, with urea nitrogen (9.3 mmol/L), creatinine (123 µmol/L), and lactate dehydrogenase (397 U/L) increased slightly. Serum sodium and chlorine levels remained normal. No bacteria, fungi, or acid-fast bacilli were detected in left, right aerobic or anaerobic blood cultures. The cerebrospinal fluid analysis results (including routine, biochemical, and culture factors) were normal, and no Cryptococcus neoformans was present.



[Table/Fig-1]: Ultrasound images showing an enlarged prostate with a calcification focus suggesting urinary tract infection.

Clinical syndromes from organic infections were excluded upon neurological examination, head magnetic resonance imaging, cerebrospinal fluid analysis, urine analysis, and blood cultures. Moreover, olanzapine-associated central anticholinergic syndrome was excluded, given the absence of dry skin/mouth, dilated pupils, and urinary retention and the presence of muscle rigidity. Finally, serotonin syndrome was excluded because of the lack of use of two or more serotonin drugs. The final diagnosis was NMS, based on the symptoms of hyperthermia, muscle rigidity, changes in mental status, autonomic activation and instability, and CK elevation of at least four-fold the upper limit of normal after using olanzapine [1].

The patient was returned to the medical ward and treated with the following: bromocriptine (1.25–2.5 mg/day for 23 days), antibiotics (cefoperazone sodium and sulbactam sodium 6 g/day for 10 days), and intravenous fluids. On day 8, his renal function returned to baseline levels and CK decreased to 1,524 U/L. Despite improved muscle tone, the patient remained in the medical ward due to fever, excessive and difficult-to-expectorate phlegm, and mental weakness. After two weeks, the patient returned to the psychiatric ward for further inpatient treatment.

On transfer to the psychiatric ward, the patient was hypomanic and not confusional. Psychiatric assessments were performed because of his previous dose-related drug reactions, which indicated that monotherapy with the drug quetiapine was acceptable. At week three after NMS recovery, quetiapine monotherapy was initiated at 25 mg and gradually increased to 600 mg (two oral doses).

Close monitoring revealed improved mental state in the patient, who was discharged 3.5 months after admission. Patient was followed up every two weeks via telephone and was instructed to take medicine (quetiapine) regularly and to see the doctor once a month. Moreover, the patient care and assistance team, composed of mental health prevention and control personnel, police officers, civil affairs officers, full-time commissioners for the disabled, family members, and volunteers, conducted home visits and follow-up with the patient every 90 days. The condition of the patient was reportedly stable, with no obvious adverse drug reactions. All examination indicators remained within normal ranges, and the patient was able to work.

DISCUSSION

The NMS, an idiosyncratic adverse reaction to typical antipsychotic medication, is caused by sudden dopamine activity reductions from dopamine antagonist exposure/agonist withdrawal [2], commonly occurring as a reaction to first-generation antipsychotics [3]. However, NMS is rarely reported with olanzapine, risperidone, paliperidone, aripiprazole, ziprasidone, amisulpride, quetiapine, and clozapine treatments [4], occurring in 0.02-3.2% of patients taking neuroleptic medication [5] and presenting similarly to other high mortality/renal failure risk-involving conditions. Fever, muscle rigidity, autonomic dysfunction, and mental state alterations are characteristic but not always present [6]. Diagnosis criteria include fever over 39°C and rigidity or CK alterations without rigidity. The Diagnostic and Statistical Manual of Mental Disorders includes hyperthermia above 38°C with profuse diaphoresis and generalised rigidity [1,7].

The NMS should be suspected in patients taking psychotropic medications and presenting similar symptoms as described here, including autonomic dysfunction, mental-state changes, fever, and muscle rigidity [8,9]. NMS exhibits a lower incidence, lower clinical severity, and less-frequent lethal outcomes when induced by second- than first-generation antipsychotics [10]. The former mostly reflect atypical NMS; cases without rigidity/fever receive probable/indefinite diagnosis [4,11]. NMS should be conceptualised as symptom spectrums rather than diagnostic criteria. This case exhibited myotonia later than fever and the severity was underestimated.

Antipsychotic drug-induced abrupt, profound dopamine D2 receptor blockades purportedly induce NMS [12,13]. Risks are associated with first-generation antipsychotics, high doses and parenteral administration of these drugs, male sex, agitation, exhaustion, dehydration, and neurological defects [14]. NMS can occur upon treatment with atypical antipsychotic drugs like olanzapine [3,14,15], particularly in the presence of risk factors. Although our patient was stable, he experienced drug-induced hyponatraemia, reduced physical strength, hypochloraemia, and fever-related dehydration affecting olanzapine metabolism, causing NMS. Olanzapine is a 5-HT2A- and D2-receptor antagonist metabolised through CYP1A2 (oxcarbazepine-mediated CYP1A2 inhibition is rare) [16,17]. The disease progressed with hyponatraemia, hypochloraemia, and threats to life without consciousness disturbance, limb convulsions, nausea, vomiting, or visual impairment. Hyponatraemia- and hypochloraemia-induced psychiatric symptoms, as well as osmotic demyelination syndrome [18], were excluded because of a lack of pontine abnormalities and NaCl supplementation. On deterioration, the psychiatric team diagnosed the patient with NMS [6] and discontinued olanzapine. After considering pneumonia/malignant syndrome, the medical team supported the NMS diagnosis.

The patient's condition improved upon drug withdrawal/treatment. Bromocriptine should be administered through gastric feeding tubes; 2.5 mg per 8 hours, increased to 5 mg every 8 hours, or 2.5 mg three times per day, and gradually increased to 2.5-7.5 mg to 45 mg daily to prevent rhabdomyolysis, dehydration, and electrolyte imbalances.

The diagnosis was consistent with clinical presentation and laboratory abnormalities, although the initial presentation was atypical. Causality was assessed using the World Health Organisation-Uppsala Monitoring Centre and Naranjo scales. The probability of eight indicated that his side effects were likely related to olanzapine [14].

CONCLUSION(S)

Given the rarity of NMS, clinicians, including psychiatrists, may never encounter/understand atypical presentations that are difficult to distinguish from other disorders. Subspecialty collaboration can ensure accurate treatment. Through professional learning and training, clinical experience, and communication among peers, psychiatrists can enhance their attention to NMS and related identification ability.

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