Case report on clozapine-associated neuroleptic malignant syndrome

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Abstract: This article summarizes the clinical manifestations of one case of clozapine-associated neuroleptic malignant syndrome and discusses its diagnosis, predisposing factors and treatment based on a literature review. Early identification and treatment is critical to lower the mortality of clozapine-associated neuroleptic malignant syndrome.

1. Case history

A 43-year-old female patient with a diagnosis of paranoid schizophrenia who had suffered from persecutory delusions for 23 years and been repeatedly hospitalized had been stable for over a year on combined treatment with 200mg per day of clozapine and 400mg per day of sulpiride. She relapsed in January 2011 and was rehospitalized on February 11, 2011 at which time she was diagnosed with paranoid schizophrenia, grade III hypertension, and type II diabetes mellitus. She had hallucinations and delusions on admission and refused to eat or take her medication; she had normal routine blood results and her liver and kidney function tests (CK, creatine kinase; LDH, lactate dehydrogenase, etc.) were within normal limits but she had high blood glucose (8.01 mmol/l). In addition to fluid replacement she was treated with clozapine (250–275 mg once daily), captopril (25 mg three times daily), felodipine (5 mg once daily), and metformin (0.25 mg twice daily).

Four days later she developed altered consciousness and impaired orientation. Magnetic resonance imaging of her head showed no obvious abnormalities so cerebral organic disease was ruled out. On February 17 she developed hypermyotonia, tremors, diaphoresis and lapsed into unconsciousness. On physical examination she had a body temperature of 38.5°C, pulse rate of 106 beats/min, respiratory rate of 20/min, and blood pressure of 160/100 mmHg. Electrocardiography revealed sinus tachycardia. Chest auscultation revealed scattered moist rales in both lungs, especially in the right lung. Biochemical test results showed significantly increased CK (1555 u/L) and LDH (723 u/L), but blood glucose and other parameters were within normal limits. Routine blood tests showed a white blood cell count of 6.54×10^9/L, neutrophils of 73.9%, and a red blood cell count of 3.76×10^12/L. Anteroposterior chest X-ray revealed thickened pulmonary markings and slight mottling with unclear edges in the right lower lobe. Blood gas analysis results were normal.

Neuroleptic malignant syndrome (NMS) accompanied by pulmonary infection was highly suspected. Clozapine was stopped, massive fluid supplementation was provided, basic nursing care was enhanced, and cefminox was administered to treat the suspected lung infection. On February 18 her body temperature returned to normal and her hypermyotonia, tremor and diaphoresis improved but her consciousness remained impaired. On February 19 the patient regained consciousness, her vital signs stabilized, and her other physical symptoms resolved, but her hallucinations and delusions persisted. Laboratory tests on February 23 showed that all biochemical parameters had returned to normal levels. She was then restarted on antipsychotic medications, initially with olanzapine at a dose of 5mg once daily that was subsequently increased to 20mg once daily. She was discharged one month later and eight months after discharge she remained stable and able to engage in regular activities while receiving outpatient treatment and taking a daily dose of 15mg of olanzapine. No unexplained fever, increased muscle tension, confusion or other symptoms were observed after discharge.

2. Discussion

NMS, first reported by Deley in 1960,[1] is a rare, life-
threatening neurological disorder most often caused by an adverse reaction to antipsychotic medications. The mean incidence of NMS is 0.2%. There are no widely accepted criteria for NMS but most clinicians base their diagnosis on the criteria proposed in DSM-IV: (a) Development of severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication. (b) two or more of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, changes in the level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, or laboratory evidence of muscle injury (e.g., elevated CK). And (c) the symptoms cannot be better explained by the use of other medications or by a neurological or other general medical condition. Clinically, most patients with NMS do not meet full criteria, possibly because the condition is usually detected and treated in its early stages so it does not have the opportunity to progress to the full-blown syndrome.

NMS should be suspected whenever a patient taking antipsychotic medication develops myotonia and confusion. The clinical manifestations in this patient met these basic criteria but the patient did not have an elevated white blood count (possibly due to the inhibitory effect of clozapine). There was, however, a marked increase in the proportion of granulocytes, hypermyotonia, disturbed consciousness, and autonomic dysfunction, all of which are strongly suggestive of NMS, particularly in the presence of a relatively rapid increase in the dose of clozapine. A potential differential diagnosis in the patient was pulmonary encephalopathy secondary to the lung infection. There was, however, no clear hypoxia or carbon dioxide retention seen in the blood gas analysis, so the possibility of pulmonary encephalopathy was ruled out.

The development of NMS is closely associated with medication use and with the characteristics of the affected patient. It is believed the occurrence of NMS is more common when using high-potency antipsychotic medication, especially long-acting preparations, but the risk of NMS is not associated with the accumulated lifetime dosage or with the method of administration of the medication. Haloperidol has been most frequently associated with NMS and is thought to confer the greatest risk, but most researchers believe that almost all antipsychotic medications can induce NMS. In patients with active psychiatric symptoms and a chronic disease course, factors such as hyperexcitation, prolonged sleeplessness, malnutrition, food refusal, and dehydration can trigger NMS. The patient described in this case report was in an active phase of a chronic mental illness; her poor appetite, malnutrition, and the accompanying lung infection may have all contributed to the development of NMS.

For patients susceptible to NMS clinicians should first meet their physiological needs by improving their fluid balance and nutritional status; ideally antipsychotic medications should only be considered after the patient’s physiological status has returned to normal. If the symptoms and signs of NMS are identified, all antipsychotic drugs should be stopped, basic nursing should be enhanced, and the symptoms should be managed by physical cooling, fluid supplementation, and anti-infective therapies. Dopamine receptor agonists such as bromocriptine and amantadine may be administered but this should be done cautiously while monitoring blood pressure because high-dose bromocriptine may worsen psychiatric symptoms and lower blood pressure. Electroconvulsive treatment (ECT) is reportedly a relatively safe therapy for NMS and it has been used for this condition in China, but this should also be done cautiously because even modified ECT can increase the risk of severe rhabdomyolysis in patients taking succinylcholine, especially those with cardiovascular diseases or hyperkalemia. For NMS patients with multiple organ failure the augmentation of ongoing anti-infective treatment with hemopurification can be effective in controlling the azotemia and in maintaining the water, electrolyte, and acid-base balance.

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