A case of neuroleptic malignant syndrome induced by perospirone

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Summary: Neuroleptic malignant syndrome (NMS) is a rare but life-threatening condition induced by neuroleptic medications. Its main symptoms include the rapid onset of fever, severe extrapyramidal symptoms, autonomic nervous system dysfunction, and impaired consciousness. In severe cases, acute renal failure and circulatory failure can develop, which can rapidly lead to death. In this case report, we discuss the etiology, pathophysiology and management of this condition in a female patient with NMS induced by perospirone. The case highlights the need for clinicians to be vigilant: rapid identification of NMS and vigorous symptomatic treatment of NMS symptoms is the key to decreasing the case-fatality of this rare but serious adverse reaction to antipsychotic medications.

1. Case history
A 40-year-old female sought outpatient treatment at the Third People’s Hospital of Huzhou City in March 2011 for auditory verbal hallucinations and persecutory delusions. She had a family history of schizophrenia, but was otherwise healthy. She was diagnosed with schizophrenia and prescribed olanzapine 5 mg/d. During the first week of treatment her dosage was increased to 10 mg/d but at this dose she experienced akathisia and other extrapyramidal symptoms. Adjunctive treatment with trihexyphenidyl 6 mg/d only partially ameliorated this adverse effect. Nevertheless, after two weeks of treatment her olanzapine was increased to 20 mg/d and she subsequently stayed on this dosage for a further five weeks. By this time (seven weeks after starting treatment), most of her psychotic symptoms had resolved. After three months of treatment her symptoms were completely under control so her maintenance dosage was reduced to olanzapine 15 mg/d and her trihexyphenidyl was subsequently stopped because her extrapyramidal symptoms had disappeared.

After one year on this maintenance dosage of olanzapine, she developed symptoms of metabolic syndrome including obesity, elevated blood glucose and elevated blood lipids. She stopped her olanzapine because of these symptoms, but she had a relapse of her psychotic symptoms one month later. She returned to our outpatient department for treatment in October 2012. She was started on an initial dosage of risperidone 2 mg/d, which was gradually increased to 6 mg/d over the first two weeks of treatment. Her psychotic symptoms were significantly improved but she subsequently developed extrapyramidal symptoms and tachycardia, which abated after starting adjunctive treatment with trihexyphenidyl 6 mg/d and propranolol 20 mg/d. After three months on these medications, her metabolic symptoms subsided but she developed menstrual irregularity and lactation. The risperidone was subsequently reduced to a maintenance dosage of 4 mg/d. This maintained control of her psychotic symptoms but after six months on this maintenance regimen she reported low libido and intolerable anxiety and restlessness.

To help adjust her medications, she was admitted to an inpatient psychiatric ward in July 2013. On admission her routine blood tests, liver and renal function tests, electrocardiogram, chest X-ray and other lab tests were all normal. Her antipsychotic medication was converted from risperidone to perospirone. She was given perospirone 8 mg/d during the first week of admission while the risperidone was tapered and then stopped; during the second week of admission the perospirone dosage was gradually increased to 24 mg/d. However, this dosage of perospirone was insufficient to control her psychotic symptoms. She again reported auditory hallucinations and persecutory delusions, her eating became erratic, and she became impulsive and irritable. In the third week of admission the dosage of perospirone was gradually increased to 40 mg/d. This dosage controlled the psychotic symptoms but on 16 August she developed tremor, muscle rigidity, akathisia, and other extrapyramidal symptoms. Adjunctive treatment with trihexyphenidyl 8 mg/d was initiated, but this did not ameliorate the extrapyramidal symptoms. Two days later (on 18 August) she suddenly developed heavy sweating, difficulty swallowing and speaking, elevated muscle tension, tachycardia, fluctuating blood pressure, and a fever of 39.8 °C. She was extremely restless and...
confused. Neuroleptic malignant syndrome (NMS) was considered. The perospirone was stopped immediately. Results of a routine blood test showed elevated white blood cells (18.3 x 10^9/L; normal range: 4.0-10.0 x 10^9/L). Blood chemistry revealed low serum sodium (129 mmol/L; normal range: 135-145 mmol/L), low serum potassium (3.2 mmol/L; normal range: 3.5-5.5 mmol/L); elevated serum creatine phosphokinase (CPK, 813.2 U/L; normal range for women: 26-140 U/L), and elevated serum myoglobin (486 μg/L; normal range for women: 12-76 μg/L). After emergency consultation with a neurologist, a lumbar puncture was performed to exclude the possibility of encephalitis; examination of the extracted cerebrospinal fluid found no abnormalities. Neuroimaging did not identify any abnormalities. Electroencephalography (EEG) demonstrated diffuse slow waves, consistent with metabolic encephalopathy.

The diagnosis was established in consultation with senior clinicians at the hospital: NMS induced by atypical antipsychotic medication. The patient, who was now unconscious, was in a critical condition. She was given level I care which included nasal feeding, liquid diet, continuous oxygen therapy, and electrocardiographic monitoring. Ice pillows and ice packs were used to lower her temperature. To treat the NMS symptoms she was given 10 mg/d diazepam intravenously, 40 mg/d bromocriptine orally (a dopamine agonist), and 200 mg/d dantrolene orally (a muscle relaxant). Supportive treatment was also provided to keep her airway clear, maintain hydration, stabilize blood pressure, restore electrolyte balance, prevent infection, and prevent damage to the liver or kidney. On August 21st, three days after her full-blown NMS symptoms began, her condition started to stabilize. On August 25th she gradually regained consciousness, her muscle tension slowly became normal, and her vital signs were basically stable. Two weeks after recovering from the NMS, risperidone 4 mg/d was re-introduced. She experienced side effects similar to the last time that she took risperidone (i.e., decreased libido, anxiety and restlessness), but these symptoms were partially ameliorated by psychological counseling.

2. Discussion

NMS was first reported by Deley and colleagues in 1960. [1] The incidence of NMS is 0.1 to 1% and the mortality rate is 20 to 30%. [2] The onset of NMS is usually acute, and the symptoms are complex and atypical, so it is difficult to diagnose. The diagnostic criteria for NMS in DSM-IV-TR [3] are as follows: severe muscle rigidity and elevated body temperature after the recent use of antipsychotic medications in an individual who concurrently exhibits two or more associated symptoms including diaphoresis, dysphagia, tremor, incontinence, altered mental status (from mild confusion to coma), mutism, tachycardia, elevated or unstable blood pressure, raised leukocyte level, and laboratory evidence of muscle damage (such as increased CPK). To make the diagnosis the clinician must ascertain that the symptoms cannot be explained by other drugs, neurological diseases, physical illnesses, or another mental disorder.

Risk factors of NMS include agitation, dehydration, the use of physical restraints, pre-existing abnormality of dopamine activity and receptor functioning in the central nervous system, and iron deficiency. [13] In almost all cases, NMS is preceded by physical exhaustion or dehydration. [6] In some cases, increase in the ambient temperature is a risk factor. [14] Fifteen to 20 percent of patients with NMS have a previous history of NMS. [7] Almost all of the dopamine antagonists are associated with NMS; high-potency drugs have a higher risk of inducing NMS than low-potency drugs and atypical antipsychotics. [4] Parenteral administration of antipsychotic medication, abrupt changes in dosage, and high dosage are also risk factors of NMS. [6] When using antipsychotic medications to treat delirium, the risk of NMS is increased. [8]

The mechanism of NMS is related to the strong affinity of antipsychotic medications to dopamine receptors. Antipsychotic medications can completely occupy the dopamine receptors, preventing their normal function of combining with dopamine and, thus, block dopaminergic neurotransmission. [9] The medications act on the autonomic nervous system by blocking peripheral adrenergic receptors and cholinergic receptors which results in hypotension, tachycardia, urinary incontinence and other symptoms of autonomic nervous system dysfunction. The medications also act on the thermoregulatory mechanism in the hypothalamus, resulting in a persistently high body temperature. [4] Some research suggests that risk of NMS may be partly determined by genetic factors. [10]

NMS symptoms can resemble those seen in some other conditions so clinicians need to carefully consider the differential diagnosis. (a) Central nervous system (CNS) infections – especially viral encephalitis – can result in some of the symptoms that are characteristic of NMS but, unlike NMS, the prodromal symptoms of viral infections often include headache, meningeal irritation, seizure, changes in the cerebrospinal fluid, and localizing neurological symptoms. [4,11] (b) Malignant hyperthermia shares two core symptoms with NMS – hypothermia and muscle rigidity [12,15] – but, unlike NMS, the other common symptoms of malignant hyperthermia include hemoglobinuria, myoglobinuria, heart abnormalities (induced by hyperkalemia), and cyanosis. [14] Moreover, malignant hyperthermia usually develops during surgery (caused by an inhaled anesthetic) in individuals with a history of primary musculoskeletal disorders. [15] (c) Persistent non-convulsive seizures and structural lesions affecting the midbrain and brain stem can also exhibit symptoms that mimic those seen in NMS. [4]

Treatment for NMS primarily involves immediate discontinuation of antipsychotic medications and symptomatic treatment of the specific symptoms. In the acute phase, patients with NMS experience fever and dehydration, thus the key intervention includes rehydration and correction of electrolyte imbalances. If renal failure occurs, hemodialysis can be used. Because
of the dysfunction of the thermoregulatory center, antipyretic drugs are generally ineffective, so body temperature needs to be lowered with ice pillows and ice packs over the whole body. Some reports suggest that electric shock therapy is effective for patients with NMS who do not respond to other methods.\cite{16}

In the present case, the patient developed NMS after taking perospirone, a novel atypical antipsychotic medication that produces its antipsychotic effects by blocking both the central 5-hydroxytryptamine-2 receptor (5-HT2) and the dopamine-2 receptor (D2).\cite{17} Perospirone can be absorbed quickly after oral intake, has a high bioavailability and a short half-life. It is decomposed through the liver, thus the metabolites are primarily excreted in the urine, and the excretion is easy. The common side effects of perospirone include akathisia, tremor, muscle rigidity, insomnia, drowsiness and other neuropsychiatric symptoms. There are few reports about NMS induced by perospirone; the reported incidence is 0.1 to 5%.\cite{16} The symptoms that occur in perospirone overdose are not clear.

There are several possible precipitants of our patient’s episode of NMS. Her overall diet prior to developing NMS was poor because she had refused to eat (due to persecutory delusions). She was exhausted, dehydrated and had imbalanced electrolytes. She had recently changed medication (from risperidone to perospirone) and had had a relatively rapid increase in dosage. It was, moreover the peak of summer, so the ambient temperature and humidity were quite high. All of these factors have been identified as potential precipitants of NMS in the literature.\cite{14,6}

Rapid identification of the patient’s condition and vigorous symptomatic treatment lead to a gradual return to normal functioning about three days after the NMS episode started. Clearly, the key to reducing fatalities among patients who develop NMS after use of antipsychotic medication is for clinicians to be vigilant and, when the diagnosis is suspected, to take rapid action to aggressively treat the life-threatening symptoms.

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The patient described in this case report provided written consent to publish the report.

Conflict of interest

The authors report no conflict of interest.

References

1. Deley J, Picht P, Lemperiere T, et al. Un neuroleptique majeur non-phenothiazine et nonreserpinique, l’haloperidol, dans le traitement des psychoses. Annales Medpsychologique 1960; \textbf{118}(1): 145-152. (in French)

2. Shen YT. Psychiatry, 5th edition. Beijing: People’s Health Publishing House; 2009. p. 838-839. (in Chinese)

3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.

4. Strawn JR, Keck PE Jr, Caroff SN. Neuropsychiatric malignant syndrome. Am J Psychiatry \textbf{2007}; \textbf{164}(6): 870-876.

5. Keck PE, Pope HG, Cohen BM, McElroy SL, Nierenberg AA. Risk factors for neuroleptic malignant syndrome. A case-control study. Arch Gen Psychiatry 1989; \textbf{46}(10): 914-918.

6. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull \textbf{1988}; \textbf{24}(1): 25-29.

7. Caroff SN, Mann SC. Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: case reports and a review of the literature. Psychosomatics \textbf{2009}; \textbf{50}(1): 8-15.

8. Seitz DP, Gill SS. Neuroleptic malignant syndrome: implications for antipsychotic therapy. Am J Pharmacogenomics \textbf{2003}; \textbf{3}(2): 89-95.

9. Meng JM. New Clinical Developments in Neurology. Beijing: Beijing Publishing House; 1994. p. 285-303. (in Chinese)

10. Gronert GA. Malignant hyperthermia. Anesthesiology \textbf{1980}; \textbf{53}(3): 395-423.

11. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med \textbf{2000}; \textbf{352}(11): 1112-1120.

12. Heiman-Patterson TD. Neuroleptic malignant syndrome and malignant hyperthermia. Important issues for the medical consultant. Med Clin North Am \textbf{1993}; \textbf{77}(2): 477-492.

13. Zhou XD, Hu, GX, Liu ZY, Shi JX. Introduction of a new antipsychotic - perospirone hydrochloride. Medical & Pharmaceutical Journal of Chinese People’s Liberation Army \textbf{2011}; \textbf{23}(1): 64-66. (in Chinese)

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