Neuroleptic malignant syndrome: case report and discussion

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Abstract

WE REPORT A CASE INVOLVING AN 81-YEAR-OLD man with schizoaffective disorder who presented with neuroleptic malignant syndrome (NMS) after an increase in his neuroleptic dose. NMS, a rare but potentially fatal complication of neuroleptic medications (e.g., antipsychotics, sedatives and antinauseants), is characterized by hyperthermia, muscle rigidity, an elevated creatine kinase level and autonomic instability. The syndrome often develops after a sudden increase in dosage of the neuroleptic medication or in states of dehydration. Treatment is mainly supportive and includes withdrawal of the neuroleptic medication and, possibly, administration of drugs such as dantrolene and bromocriptine. Complications of NMS include acute renal failure and acute respiratory failure. Given the widespread prescription of neuroleptics by physicians in a variety of fields, all physicians need to be able to recognize and appropriately manage NMS.

Case

An 81-year-old man with a history of schizoaffective disorder presented to hospital with increasing auditory hallucinations, persecutory delusions and depressive symptoms, including suicidal ideation. He was admitted to hospital and given loxapine (10 mg every morning, 50 mg every evening) for his psychotic symptoms and methotrimeprazine (10 mg once daily) for sleep disturbance. Two weeks earlier he had been prescribed venlafaxine by his family physician and had been experiencing some symptomatic hypotensive episodes as a result. He had also been taking levothyroxine (0.1 mg once daily) and procyclidine (2.5 mg once daily).

Within 3 days after admission, the methotrimeprazine therapy was stopped because of somnolence and the loxapine dose increased to 65 mg/d at bedtime. Twelve hours after this change, the patient had diaphoresis, tremulousness, urinary incontinence and some cognitive impairment. His temperature was elevated (38.3°C), and although normotensive (blood pressure 124/84 mm Hg) he had tachycardia (heart rate 128 beats/min) and exhibited Parkinsonian features, including tremor, rigidity and unsteady gait. An electrocardiogram revealed no acute ischemic changes. Laboratory investigation revealed mild leukocytosis (leukocyte count 11.7×10^9/L), with a shift to the left (neutrophil count 9.9×10^9/L). His aspartate aminotransferase level was elevated (82 U/L), and his creatine kinase (CK) level was markedly elevated (1145 U/L), with normal CK MB fraction and cardiac troponin levels. Other laboratory results, including electrolyte levels, were normal.

The patient was observed for the night. The next morning his Parkinsonian features and elevated temperature persisted, and he was found to have bilateral hyporeflexia. The loxapine therapy was stopped because neuroleptic malignant syndrome (NMS) was suspected. That afternoon the CK level climbed to 2574 U/L. The next day, the patient had increased rigidity and his temperature rose to 39.3°C. A septic workup yielded normal results, but the urine myoglobin test result was positive. A firm diagnosis of NMS was made, and therapy with dantrolene (70 mg intravenously) was started and about 24 hours later was changed to bromocriptine (2.5 mg 3 times daily).

Within a few days, the patient's NMS symptoms improved and his CK level returned to normal. As his symptoms resolved, the bromocriptine dose was tapered off. In order to control his ongoing psychotic symptoms, the patient was prescribed olanzapine (2.5 mg once daily) because of its lower reported rate of NMS. He was also given sertraline (25 mg once daily) to control his depressive symptoms. After 5 weeks, his depressive and psychotic symptoms improved considerably, and he was discharged from hospital without further complications.

Comments

NMS is an uncommon but serious complication of neuroleptic medications. It was first described in 1967 as "akinetic hypertonic syndrome."[1,2] The frequency of the syndrome ranges from 0.07% to 2.2% among patients receiving neuroleptic medications.[1] The mortality is 10%–30%.[1]

NMS likely results from a complex interaction between the neuroleptic medication and a susceptible host. Two theories have been proposed to explain the syndrome: central dopamine receptor blockade and skeletal muscle defect. In the first theory, the dopaminergic receptor antagonism by neuroleptics may interfere with dopamine's normal role in central thermoregulation. Heat is produced from serotonin stimulation in the hypothalamus, and dopamine inhibits this process. Dopaminergic blockade therefore leads to less inhibition of serotonin stimulation and contributes to the hyperthermia seen in NMS.[3] To support this theory, there have been reported cases of conditions resembling NMS in patients with Parkinson's disease who had no history of the syndrome and in whom therapy with levodopa–carbidopa

Box 1: Neuroleptic medications associated with neuroleptic malignant syndrome (NMS)*

Typical neuroleptics	*Atypical neuroleptics*
• Haloperidol (+++)	Clozapine (+)
• Chlorpromazine (++)	Olanzapine (+)
• Fluphenazine, long acting (++)	Quetiapine (+)
• Fluphenazine (++)	Risperidone (+)
• Levomepromazine (+)	
• Loxapine (+)	

*+ = rarely associated with NMS, +++ = more commonly associated with NMS.[1,8–14]

and amantadine was abruptly stopped.[4] Because central thermoregulation is mediated by noradrenergic, dopaminergic, serotoninergic and cholinergic pathways, it is unlikely that the syndrome is due to central dopaminergic blockade alone.[1] Furthermore, dopamine may directly inhibit skeletal muscle contraction, and therefore dopamine blockade may result in increased skeletal muscle contraction.[5]

In the second theory, NMS is believed to share a pathophysiology with malignant hyperthermia.[6] The symptoms of hyperthermia, rigidity and elevated CK levels are common to both conditions, as is the response to the peripheral muscle relaxant, dantrolene. Furthermore, both conditions produce abnormal in vitro contractility test results.[1,7] As has been found in patients with malignant hyperthermia, in vitro investigations of patients with NMS have revealed multiple defects in skeletal muscle, usually associated with increased calcium release from the sarcoplasmic reticulum.[5]

Most neuroleptic medications have some risk of NMS associated with them (Box 1).[1,8–14] Even atypical neuroleptics previously thought to have less risk, such as olanzapine[13,14] and quetiapine,[8] have been associated with reported cases of NMS. A rapid change in neuroleptic dose is a major risk factor for the syndrome,[15] especially if it occurs within 5 days before the onset of symptoms,[16] and the risk can persist for 20 days or more after discontinuing the neuroleptic therapy.[1] NMS most often occurs after the initiation or increase in dose of neuroleptics, but rarely it can occur after the sudden discontinuation of the drug therapy.[17] There is no demonstrable relation between the actual dose or duration of exposure of the neuroleptic and the development or fatal outcome of NMS.[18] There seems to be no significant difference in the duration of clinical symptoms with long-acting neuroleptics compared with short-acting ones.[18] Psychomotor agitation preceding the onset of symptoms is a significant clinical manifestation in patients who are at risk of NMS.[15,19] Dehydration with the concomitant use of neuroleptics has been implicated as a risk factor for the syndrome, because the decreased blood volume induces peripheral vasoconstriction and impairs heat dissipation. NMS can often be prevented by ensuring that patients receiving neuroleptics are well hydrated. Other risk factors for NMS include stress, humidity and concomitant use of lithium, anticholinergic agents or some antidepressants.[9]

Many diagnostic criteria have been proposed for NMS, but because of its variable presentation, no single set of criteria is used universally. Some clinical manifestations are described in Box 2.[1,9,20] The symptoms usually develop over 24 to 72 hours and can last from 1 to 44 days (about 10 days on average).[13] There is no typical sequence of symptoms, but extrapyramidal symptoms usually occur before autonomic ones.[17] Hyperthermia, rigidity and recent initiation of drug therapy with one or more neuroleptics are common features of NMS.

The differential diagnosis of NMS is described in Box 3.[1,10,12,20,21] A thorough history taking, physical examination and laboratory investigations, including leukocyte count with differential, renal function tests, and measurement of electrolyte, serum CK, urine myoglobin and serum lithium concentrations, should be performed. An electroencephalogram, CT scan of the head and lumbar puncture should also be considered to rule out other causes.

For treatment, it is essential to recognize the symptoms and to stop the neuroleptic therapy immediately. Supportive therapy, such as fever reduction, hydration and nutri-

Box 2: Clinical manifestations of NMS

Physical findings

- Abnormal blood pressure (typically hypertension)*
- Altered level of consciousness*
- Chorea
- Diaphoresis*
- Fever (temperature > 38.5°C)*
- Generalized tonic-clonic seizures
- Muscle rigidity*
- Mutism
- Opisthotonos†
- Positive Babinski's sign
- Tachycardia*
- Tachypnea*
- Trismus‡

Laboratory findings

- ↑ Creatine kinase level*
- Leukocytosis, with shift to the left*
- Myoglobinuria*
- ↑ Transaminase levels

*Common finding.
†Extreme hyperextension of the body in which the head and heels are bent backward and the body is bowed forward.
‡Motor disturbance of the trigeminal nerve, especially spasm of the masticatory muscles, with difficulty in opening the mouth.

Box 3: Differential diagnosis of NMS

- Acute lethal catatonia
- ASA overdose
- Central anticholinergic syndrome
- Central nervous system infection (especially acute viral encephalitis)
- Drug interaction (e.g., between monoamine oxidase inhibitors and antidepressants or narcotics)
- Heat illness
- Heavy metal poisoning (e.g., lead, arsenic)
- Lithium toxicity
- Malignant hyperthermia
- Neuroleptic-related heat stroke
- Sepsis
- Serotonin syndrome
- Tetanus
- Thyrotoxicosis
- Withdrawal states (alcohol, benzodiazepine, barbiturate withdrawal)

tion, is important until the blood levels of the neuroleptic drug decrease. It is controversial whether specific therapies are beneficial in addition to the supportive therapy. The role of intravenous dantrolene sodium therapy, used widely in malignant hyperthermia, is unclear, but it is still administered to reduce body temperature and to relax peripheral muscles by inhibiting the release of calcium from the sarcoplasmic reticulum of muscle.[1] The recommended dose is 2 mg/kg intravenously, repeated every 10 minutes if necessary, to a maximum of 10 mg/kg daily.[1] It is only usually given in the acute stage and not continued for more than a few days. Hepatotoxic effects may occur if the daily dose exceeds 10 mg/kg.[1] Bromocriptine, a dopamine agonist, usually improves muscle rigidity within a few hours, followed by a reduction in temperature and an improvement in blood pressure.[1] Doses of 2.5–10 mg up to 4 times daily have been used with some success.[9] Hypotension is the most common adverse effect of bromocriptine therapy. It can be mild or severe, and treatment would be similar to that of other causes of hypotension. It is unknown what affects the degree of hypotension and other autonomic factors. Dantrolene and bromocriptine may be used together, without more adverse effects than with either one alone.[22] Amantadine and levadopa–carbidopa have been used successfully to reduce hyperthermia in patients with NMS.[23] Treatment of NMS must be continued for 2–3 weeks until symptoms remit. Because of possible exacerbation of NMS symptoms, dopamine antagonists such as metoclopramide should be avoided.

Many serious complications of NMS can arise and must be treated aggressively. Some common ones are described in Box 4.[1,10,12,18] Myoglobinuria, due to rhabdomyolysis, may develop and progress to acute renal failure, which would require temporary dialysis.[20] Renal failure is a strong predictor of death, with an associated mortality of 50%.[1] Acute respiratory failure, due to a pulmonary embolism or aspiration pneumonia, often requires mechanical ventilation in the intensive care unit.

Box 4: Complications associated with NMS

- Rhabdomyolysis
- Acute renal failure
- Acute respiratory failure (pulmonary embolism, aspiration pneumonia)
- Seizures
- Brain damage
- Myocardial infarction
- Disseminated intravascular coagulation
- Hepatic failure
- *Escherichia coli* fasciitis
- Sepsis

After an episode of NMS, neuroleptic therapy is still required to control the patient's psychiatric symptoms. Rechallenging the patient with the same neuroleptic drug at the same dose results in the syndrome recurring in 5 out of 6 cases.[1] The use of a lower potency neuroleptic (Box 1) is safe in 9 out of 10 cases.[18] Starting with an atypical neuroleptic such as olanzapine at a low dose and slowly increasing the dose while monitoring for signs of NMS and for control of psychotic symptoms is the safest option. The goal is to find the lowest dose necessary that will control the psychotic symptoms. It is important to prevent significant dehydration in patients taking neuroleptics in order to prevent the recurrence of NMS.

In summary, NMS is a potentially fatal complication of neuroleptic therapy regardless of the duration or dose of the drug. The mortality and morbidity associated with NMS can be decreased if one understands the role of neuroleptics in causing such a serious complication, if neuroleptic therapy is started slowly, in incremental doses, and if timely supportive therapy is provided.

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