**Clinical Practice Exam**

**A 56-Year-Old Man with Fever and Muscle Rigidity**

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**CASE PRESENTATION**

A 56-year-old man was found in bed by his daughter, unable to be aroused, with episodic left arm twitching. Emergency medical services were called, and the patient was given 5 mg Valium (diazepam) and 4 mg Narcan (naloxone) with no improvement in consciousness. His daughter reported that the patient had admitted to ingesting unknown amounts of Mellaril (thioridazine). Past medical history was significant for chronic obstructive pulmonary disease and hypertension, for which he was taking Calan (verapamil) 180 mg daily.

Vital signs recorded in the emergency department included pulse, 80 bpm; blood pressure, 133/82 mm Hg; and oxygen saturation by pulse oximetry, 92% on room air. Results of the physical examination were within normal limits, except for irritability, muffled speech, and asterixis present with outstretched hands.

Laboratory and imaging studies taken at admission to the intensive care unit, including complete blood count, a metabolic panel, serum and urine alcohol and toxicology screens, computed tomographic scan of the brain, and electrocardiogram, showed normal results. Leukocyte count was 10.0 $\times$ 10$^3$/mm$^3$.

Over the next 24 hours, the patient’s behavior was labile; severe agitation and waxing and waning in his level of alertness required 4-point restraints. Because of continued agitation, intravenous (IV) haloperidol in 5 mg aliquots was prescribed as needed. The patient received a total of 30 mg of IV haloperidol over the next 7 hours, at which time his level of consciousness was noticed to have significantly decreased. His heart rate at this time was 166 bpm, temperature was 39.6°C, and blood pressure was 178/83 mm Hg. On examination, peripheral muscle rigidity and urinary incontinence were noted. Laboratory findings at this time were significant for leukocytosis (19.87 $\times$ 10$^3$/mm$^3$) and elevated venous lactate (26.1 mg/dL, [2.9 mmol/L]). Creatine kinase level increased from 835 to 1749 U/L over the next 18 hours. An electrocardiogram revealed sinus tachycardia. An electroencephalogram was read to be within normal limits.

**WHAT IS YOUR DIAGNOSIS?**

A) Heat stroke  
B) Lethal catatonia  
C) Malignant hyperthermia  
D) Neuroleptic malignant syndrome

**WHAT IS THE APPROPRIATE TREATMENT?**

A) IV fluids  
B) Cooling blankets  
C) Dopamine agonists  
D) Dantrolene sodium  
E) All of the above

**ANSWERS**

The correct answers are neuroleptic malignant syndrome (D) and all of the above (E).

**DISCUSSION**

Neuroleptic malignant syndrome (NMS) is characterized by a constellation of signs and symptoms that are believed to be a direct result of treatment with neuroleptic agents. Data from retrospective studies show a prevalence of 1.4% and incidence of 2.4%. Increased awareness of this syndrome among clinicians has resulted in decreased mortality rates—from 25% before 1984 to 11.6% between 1984 and 1992.

**Clinical Manifestations**

Although NMS presents with diverse features, its...
major clinical manifestations appear to be pseudo-
parkinsonism, hyperthermia, altered mental status,
and autonomic dysfunction. Rigidity and extrapyrami-
dal symptoms usually precede body temperature eleva-
tions. Common autonomic dysfunctions include hy-
pertension and/or labile blood pressure, tachycardia,
and prominent diaphoresis. Diagnostic criteria for
NMS are provided in Table 1.

NMS may develop as quickly as 45 minutes after ini-
tiation of neuroleptic therapy or after a rapid increase
in dose of a neuroleptic agent. It has been reported,
albeit less frequently, to develop after administration of
any of the newer atypical antipsychotics, as well.2 It has
also been reported in patients treated with lithium and
in others after use of cocaine.3 Psychiatric illness does
not appear to be a prerequisite for NMS,3 although
some authors believe that affective disorder may place
patients at higher risk, perhaps as a result of medica-
tion combinations.4 Other risk factors for development
of NMS include agitation, severe debilitation, concur-
rent or organic disease, dehydration, and physical ex-
haustration.5 Agitation, confusion, or mental disorganiza-
tion may be prodromal for NMS, particularly in the
presence of musculoskeletal rigidity and mutism.6

Laboratory findings in patients with NMS usually
include significant elevation of muscle-type serum crea-
tine kinase (CK-MM), a result of myonecrosis caused by
intense and sustained muscle contractions.7 Myoglo-
binuria may occur, with the risk of acute renal failure
and death. Other laboratory findings may include leuko-
cytosis; reduced serum iron level; hyperkalemia; hypo-
and hypernatremia; and elevated aminotransferases, lac-
tic dehydrogenase, and alkaline phosphatases.

Differential Diagnoses

Extrapyramidal symptoms accompanied by fever are
very likely to be misdiagnosed as NMS. It is therefore
important to rule out other medical causes of fever in
the initial evaluation. Other important differential
diagnoses include heat stroke, lethal catatonia, and
malignant hyperthermia.

Heat stroke occurs when the temperature and
humidity in the environment are high, resulting in dis-
ruption of both central and peripheral thermoregula-
tory mechanisms. Neuroleptic treatment may, in and
of itself, predispose to heat stroke.8

Lethal catatonia is a syndrome characterized by
extreme behavioral agitation and fever, followed by

Table 1. Criteria for Diagnosis of Neuroleptic Malignant Syndrome

| Severe extrapyramidal symptoms: 2 or more of the following must be present: |
|---------------------------------|---------------------------------------------------------------|
| Lead-pipe rigidity              | Hypertension (diastolic pressure > 20 mm Hg over baseline)    |
| Pronounced cogwheeling          | Tachycardia ( > 30 bpm over baseline)                         |
| Sialorrhea                      | Tachypnea ( > 25 breaths/min)                                 |
| Oculogyric crisis               | Prominent diaphoresis                                        |
| Retrocollis                     | Incontinence                                                 |
| Opisthotonus                    |                                                               |
| Trismus                         |                                                               |
| Dysphagia                       |                                                               |
| Choreiform movements            |                                                               |
| Dyskinetic movements            |                                                               |
| Festinating gate                |                                                               |
| Flexor-extensor posturing       |                                                               |

Adapted from Marder SR. Antipsychotic medication. In Schatzberg AF, Nemeroff CB, editors. The American Psychiatric Press textbook of psy-
exhaustion and even death. It occurs in psychotic patients who have not received neuroleptics.² It is extremely important to differentiate lethal catatonia from NMS—administration of neuroleptics is a preferred treatment for lethal catatonia, whereas discontinuation of neuroleptics is required for the treatment of NMS.

Malignant hyperthermia is an inherited autosomal dominant neuromuscular disorder in which generalized contractions of skeletal muscles occur after exposure to certain muscle-depolarizing relaxants or gaseous and local anesthetics. The clinical manifestations are thought to result from an excessive influx of myoplasmic calcium and inhibition of normal contractile mechanisms.¹⁰

**Treatment**

**General considerations.** Treatment of NMS usually begins with discontinuation of neuroleptic medication. Supportive care is essential and includes lowering the body temperature, correcting electrolyte imbalances, and aggressively replacing fluids. Treatment of concomitant medical illness (eg, aspiration pneumonia, pulmonary embolism, myoglobinuria, renal failure) should be promptly addressed.

**Pharmacologic treatment.** Extrapyramidal symptoms may be treated with parenteral or oral anticholinergic agents, followed by dopamine agonists if required. The dopamine agonist bromocriptine can also be used to control agitation and coma. It is usually prescribed at 2.5 mg 3 times daily, gradually increasing to 10 mg 3 times daily if needed.⁵

Severe muscle rigidity usually responds to administration of dantrolene sodium.¹¹ Bolus injections of 1 mg/kg body weight (up to a maximum dose of 10 mg/kg body weight) can be used. Dantrolene may also be given orally, 4 to 8 mg/kg body weight daily, divided into 4 doses.

Parenteral benzodiazepines¹² as well as calcium channel blockers¹³ have been used successfully for patients requiring treatment for agitation. Benzodiazepines, working through prefrontal γ-aminobutyric acid (GABA), may reduce firing in the dopaminergic neurons of the limbic system to control psychiatric symptoms. Electroconvulsive therapy has also been beneficial for reduction of NMS symptoms in some patients.¹⁴ Electroconvulsive therapy may also assist in the control of symptoms of psychosis in patients with either affective disorder or schizophrenia.

**Reintroduction of antipsychotic agents.** After recovery from NMS, a patient requiring antipsychotic therapy should preferentially be treated with an antipsychotic drug from a different class than that which caused the NMS. However, the same drug that caused NMS may be reintroduced.¹⁵ A mandatory 2-week period without symptoms of cogwheeling or elevated temperature is necessary before the same drug is reintroduced. Depot preparations should be avoided, and dosages should start low and be advanced slowly.

Opinions vary regarding the duration of time before one should attempt reintroduction of antipsychotic drugs. Waiting 2 months before reintroducing any antipsychotic agents is a safe approach, but in some reported cases, 2 weeks was sufficient.¹⁶–¹⁸ In our experience, graphing levels of creatine kinase and body temperature for approximately 1 month following the reintroduction of antipsychotic medications has been an important means of identifying signs that may indicate relapse of NMS. Although it is a nonspecific sign (associated with the acute-phase reaction), serum iron levels fall during NMS and return to normal after the illness resolves.¹⁹

**Treatment of case patient.** The patient described was given IV fluids, and cooling blankets were applied. Haloperidol was discontinued. β-Blockers were administered to control heart rate and blood pressure. Acetaminophen was given also, which may have assisted in lowering the patient’s temperature. Diphenhydramine was given intravenously and may have helped to reduce discomfort from rigidity. Agitation control was improved with administration of low-dose lorazepam. The patient recovered completely within 48 hours (ie, normal temperature, stable vital signs, normal mental status, absence of cogwheeling or other signs of increased muscle tone). His creatine kinase level decreased to 375 U/L, which is within normal limits.

**REFERENCES**


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