Fever, Consciousness Disturbance, and Muscle Rigidity in a 68-Year-Old Man With Depressive Disorder*

Hsing-Chen Tsai, MD; Ping-Hung Kuo, MD; and Pan-Chyr Yang, MD, PhD, FCCP

(CHEST 2003; 124:1598–1601)

A 68-year-old man presented to the emergency department of our hospital because of high fever, tachycardia, consciousness disturbance, and generalized muscle rigidity. According to his caregiver's statement, he was found groaning and shivering on the bed with rapid and shallow respirations before he was sent to the hospital.

The patient had a depressive disorder and had been followed up regularly at a local psychiatric center for 6 years. Moreover, he had chronic hepatitis B and had received a diagnosis of pneumoconiosis. Ten days before this hospital admission, he was brought to the psychiatric clinic of our hospital because of deteriorating depressed mood. Venlafaxine, amantadine, clonazepam, and zopiclone were prescribed, and he had good compliance to these drugs. The patient had also received an influenza vaccination 8 h prior to this emergency visit.

Physical Examination

Temperature was 39.7°C, BP was 162/92 mm Hg, pulse rate was 142 beats/min, and respiration rate was 30 breaths/min. The patient appeared acutely ill, with sweating and severe shivering. The sclerae were not icteric. The pupils were isocoric with prompt light reflex. The neck was stiff. The neck veins were not engorged, and no lymphadenopathy was noted. Respirations were rapid and shallow, but the lungs were clear, and the heart had no murmur. The abdomen was soft and flat without tenderness. There was no hepatosplenomegaly. Persistent tremor and cogwheel rigidity of four extremities were noted. There was no pitting edema, bruise, skin rash, or wound.

Laboratory Findings

Laboratory findings were as follows: WBC count, 6,270/μL with 90% neutrophils; platelet count, 264,000/μL; hemoglobin, 12.5 g/dL; blood glucose, 256 mg/dL; sodium, 141 mEq/L; potassium, 3.88 mEq/L; total calcium 2.22 mmol/L; aspartate aminotransferase, 69 U/L; total bilirubin, 0.9 mg/L; BUN, 23.5 mg/L; creatinine, 1.3 mg/L; albumin, 4.0 g/dL; creatine kinase, 1,122 IU/L with a MB fraction of 21.5 IU/L. Arterial blood gas analysis when breathing 3 L/min of oxygen via a nasal prong showed pH 7.468, PaO₂ of 126 mm Hg, PaCO₂ of 22 mm Hg, and HCO₃⁻ of 16 mEq/L. The ammonia level was within normal limit, and the C-reactive protein was not elevated. The urinalysis was positive for occult blood, but there was no hematuria, pyuria, or ketonuria. The chest radiograph (Fig 1) was unremarkable except for bilateral interstitial infiltrates compatible with the previous diagnosis of pneumoconiosis. CT of the brain (Fig 2) was negative. A lumbar puncture yielded clear, colorless cerebrospinal fluid that contained only one lymphocyte per microliter. The open pressure was within normal limit. The glucose and total protein levels of the cerebrospinal fluid were 92 mg/dL and 67.4 mg/dL, respectively.

The patient was admitted to our ICU because of drowsy consciousness and clinical pictures mimicking systemic inflammatory response syndrome. Broad-spectrum antibiotics were administered initially but discontinued soon after the diagnosis of infection was excluded. The rhabdomyolysis was managed with vigorous hydration and urine alkalinization, as well as cautious monitoring of serum potassium and phosphate levels; however, his hyperthermia persisted despite acetaminophen, nonsteroidal anti-inflammatory drug, and ice pillow use.

What is the most likely diagnosis?
Figure 1. Chest radiograph on the first day of admission to the ICU.

Figure 2. CT of the brain.
Neuroleptic malignant syndrome (NMS) is a relatively rare but potentially fatal condition associated with the use of antipsychotic drugs. Since its first description in 1960, this syndrome has been reported among patients of all ages, and about twice as often for male as for female patients. It is not specific to any neuropsychiatric disorder. Using different diagnostic criteria, retrospective estimates of the incidence of NMS vary from 0.02 to 3.23% of psychiatric inpatients receiving neuroleptics. Patients with NMS often have a psychiatric history and present with high fever, altered mental status, muscle rigidity, autonomic dysfunction, and elevated level of creatine kinase. The hyperthermia in NMS constitutes a medical emergency and predisposes to irreversible brain damage if not reduced immediately. Generalized rigidity, described as “lead-pipe,” is a core feature of NMS, and is usually associated with myonecrosis. Cogwheeling, myoclonus, and coarse tremors are often described. Mental status changes include clouding of consciousness ranging from delirium to stupor and coma. Autonomic activation and instability are common, manifested by tachycardia, oscillations in BP, and tachypnea. These manifestations might lead to a diagnosis of systemic inflammatory response syndrome. Early recognition of the syndrome is essential because any delay in diagnosis would result in unfavorable outcome and even death.

Disorders with fever, altered mental status, and muscle rigidity that can be mistaken for NMS include infection in the CNS, malignant hyperthermia, heat stroke, lethal catatonia, rhabdomyolysis, thyroid storm, and others. Thorough physical examination and laboratory tests including CBC count, electrolytes, creatine kinase, blood culture, lumbar puncture, and image studies of the head are recommended. Until now, there has been no consensus about the diagnostic criteria of NMS, which may manifest along a symptom and severity spectrum. No laboratory abnormalities are specific or pathognomonic for the diagnosis; therefore, it is sometimes hard to make an accurate diagnosis until the syndrome is full blown.

The pathophysiology of NMS is still not fully understood. It is currently believed to be caused either by neuroleptic-induced dopamine depletion or a blockade in both the striatum and hypothalamus, leading to abnormal thermoregulation. Data on dosage indicate that NMS is not a result of overdosage with neuroleptics, and usually occurs with drug levels within the therapeutic range. It occurs idiosyncratically and develops in only a small number of patients among those who are receiving neuroleptics. Many physiologic and environmental factors were suggested to promote the occurrence of NMS, including dehydration, agitation, malnutrition, exhaustion, and IM injection of neuroleptics. Whether the syndrome has a genetic predisposition, as in the case of malignant hyperthermia, is still under investigation.

Virtually all neuroleptics are capable of inducing NMS, including phenothiazines, thioxanthenes, and the newer atypical antipsychotics, such as clozapine, risperidone, and olanzapine. In addition, NMS has also been reported in association with other drugs used in medicine that have neuroleptic properties. These include antiemetics (prochlorperazine), antispasmodic agents (metoclopramide), anesthetics (droperidol), and sedatives (promethazine). Haloperidol, used commonly in the ICUs, is high on the list among the causative medications. Venlafaxine, a selective serotonin reuptake inhibitor, has been reported to induce NMS previously. Though rare, NMS could be an adverse reaction induced by venlafaxine. The possible mechanism was proposed to be extrapyramidal side effects of selective serotonin reuptake inhibitor and the inhibitory action of serotonin on dopamine activity.

Although having a variable onset, NMS usually develops over a period of 24 to 72 h, and its clinical course runs from 2 to 14 days; however, the course of NMS may be prolonged in some cases. For example, patients receiving long-acting depot neuroleptics may remain ill nearly twice as long. Successful treatment of this syndrome depends on early recognition and prompt withdrawal of the neuroleptic agents. Supportive therapies including IV fluids, antipyretics, and cooling blanket are required. It is also important to properly position the patient to avoid aspiration due to the temporary loss of the gag reflex. Dopamine agonist medications such as amantadine should be continued if already in use, because their withdrawal may worsen the syndrome.

The benefit of adding specific pharmacotherapy to supportive measures has not been supported in clinical trials. Based on anecdotal experience in the literature, however, bromocriptine and dantrolene seem to be able to effectively shorten the time to clinical response. In addition, sodium nitroprusside infusion has been reported to be beneficial in treating severe hypertension associated with NMS, and lowering body temperature by increasing heat dissipation from the skin through vasodilatation. Nevertheless, there is no agreement on the timing and indication for the use of these medications. The treatment of NMS should be individualized and based empirically on the character, duration, and severity of clinical signs and symptoms. It is recommended that if the patient’s condition does not improve or continues to show a trend of deteriora-

Diagnosis: Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a relatively rare but potentially fatal condition associated with the use of antipsychotic drugs. Since its first description in 1960, this syndrome has been reported among patients of all ages, and about twice as often for male as for female patients. It is not specific to any neuropsychiatric disorder. Using different diagnostic criteria, retrospective estimates of the incidence of NMS vary from 0.02 to 3.23% of psychiatric inpatients receiving neuroleptics. Patients with NMS often have a psychiatric history and present with high fever, altered mental status, muscle rigidity, autonomic dysfunction, and elevated level of creatine kinase. The hyperthermia in NMS constitutes a medical emergency and predisposes to irreversible brain damage if not reduced immediately. Generalized rigidity, described as “lead-pipe,” is a core feature of NMS, and is usually associated with myonecrosis. Cogwheeling, myoclonus, and coarse tremors are often described. Mental status changes include clouding of consciousness ranging from delirium to stupor and coma. Autonomic activation and instability are common, manifested by tachycardia, oscillations in BP, and tachypnea. These manifestations might lead to a diagnosis of systemic inflammatory response syndrome. Early recognition of the syndrome is essential because any delay in diagnosis would result in unfavorable outcome and even death.

Disorders with fever, altered mental status, and muscle rigidity that can be mistaken for NMS include infection in the CNS, malignant hyperthermia, heat stroke, lethal catatonia, rhabdomyolysis, thyroid storm, and others. Thorough physical examination and laboratory tests including CBC count, electrolytes, creatine kinase, blood culture, lumbar puncture, and image studies of the head are recommended. Until now, there has been no consensus about the diagnostic criteria of NMS, which may manifest along a symptom and severity spectrum. No laboratory abnormalities are specific or pathognomonic for the diagnosis; therefore, it is sometimes hard to make an accurate diagnosis until the syndrome is full blown.

The pathophysiology of NMS is still not fully understood. It is currently believed to be caused either by neuroleptic-induced dopamine depletion or a blockade in both the striatum and hypothalamus, leading to abnormal thermoregulation. Data on dosage indicate that NMS is not a result of overdosage with neuroleptics, and usually occurs with drug levels within the therapeutic range. It occurs idiosyncratically and develops in only a small number of patients among those who are receiving neuroleptics. Many physiologic and environmental factors were suggested to promote the occurrence of NMS, including dehydration, agitation, malnutrition, exhaustion, and IM injection of neuroleptics. Whether the syndrome has a genetic predisposition, as in the case of malignant hyperthermia, is still under investigation.

Virtually all neuroleptics are capable of inducing NMS, including phenothiazines, thioxanthenes, and the newer atypical antipsychotics, such as clozapine, risperidone, and olanzapine. In addition, NMS has also been reported in association with other drugs used in medicine that have neuroleptic properties. These include antiemetics (prochlorperazine), antispasmodic agents (metoclopramide), anesthetics (droperidol), and sedatives (promethazine). Haloperidol, used commonly in the ICUs, is high on the list among the causative medications. Venlafaxine, a selective serotonin reuptake inhibitor, has been reported to induce NMS previously. Though rare, NMS could be an adverse reaction induced by venlafaxine. The possible mechanism was proposed to be extrapyramidal side effects of selective serotonin reuptake inhibitor and the inhibitory action of serotonin on dopamine activity.

Although having a variable onset, NMS usually develops over a period of 24 to 72 h, and its clinical course runs from 2 to 14 days; however, the course of NMS may be prolonged in some cases. For example, patients receiving long-acting depot neuroleptics may remain ill nearly twice as long. Successful treatment of this syndrome depends on early recognition and prompt withdrawal of the neuroleptic agents. Supportive therapies including IV fluids, antipyretics, and cooling blanket are required. It is also important to properly position the patient to avoid aspiration due to the temporary loss of the gag reflex. Dopamine agonist medications such as amantadine should be continued if already in use, because their withdrawal may worsen the syndrome.

The benefit of adding specific pharmacotherapy to supportive measures has not been supported in clinical trials. Based on anecdotal experience in the literature, however, bromocriptine and dantrolene seem to be able to effectively shorten the time to clinical response. In addition, sodium nitroprusside infusion has been reported to be beneficial in treating severe hypertension associated with NMS, and lowering body temperature by increasing heat dissipation from the skin through vasodilatation. Nevertheless, there is no agreement on the timing and indication for the use of these medications. The treatment of NMS should be individualized and based empirically on the character, duration, and severity of clinical signs and symptoms. It is recommended that if the patient’s condition does not improve or continues to show a trend of deteriora-
tion in 1 to 3 days of supportive therapy, additional pharmacologic interventions should be considered. A review of the patient’s psychiatric clinic chart revealed that the dosage of venlafaxine was increased from once to twice daily and amantadine from half a tablet tid to one tablet bid 3 days before hospitalization. NMS was diagnosed and venlafaxine was discontinued while amantadine was maintained. Bromocriptine was administered orally. IV lorazepam was administered intermittently for the control of tremors and rigidity. Sixteen hours after ICU admission, the body temperature, heart rate, and respiratory rate decreased and his muscle rigidity improved. One day later, the vital signs had almost normalized. The serum creatine kinase reached a peak level of 25,934 IU/L 1 day after ICU, but renal function remained normal. He was discharged on the seventh hospital day without any neurologic sequelae or organ dysfunction.

**Clinical Pearls**

1. NMS should be considered in the differential diagnosis of patients with a psychiatric history who present with high fever, altered mental status, muscle rigidity, autonomic dysfunction, and elevated levels of creatine kinase.

2. Several physiologic and environmental factors have been suggested as causes of NMS, including dehydration, agitation, malnutrition, exhaustion, and the IM route of neuroleptic administration.

3. Successful treatment of NMS depends on early recognition and prompt withdrawal of neuroleptic drugs. It is advisable to discontinue neuroleptics whenever NMS is suspected.

4. In addition to supportive therapies, bromocriptine, and dantrolene may shorten the time to clinical recovery.

**Suggested Reading**


