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Selected Topics: Psychiatric Emergencies

PSYCHIATRIC EMERGENCIES FOR CLINICIANS: EMERGENCY DEPARTMENT MANAGEMENT OF NEUROLEPTIC MALIGNANT SYNDROME

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CLINICAL SCENARIO

A 25-year-old man presents with a recent diagnosis of schizophrenia. He was discharged 1 week earlier from an inpatient psychiatric unit. His mother states that he has been acting “differently” for the past 2 days. He has not been “making any sense,” has felt warm to the touch, and today has been stiff and moving rigidly like a “robot.” The review of systems per his mother is negative for hallucinations since leaving the hospital and is also negative otherwise, including for symptoms of infection. On observing the patient, he is sitting quietly with minimal movements, marked diaphoresis, and a noticeable tremor. On physical examination, vital signs are temperature of 38.7°C (101.7°F), heart rate of 125 beats/min, blood pressure 168/102 mm Hg, respiratory rate 26 breaths/min, and oxygen saturation 98%. The patient is nonverbal to questioning and appears catatonic. He has generalized muscle rigidity, but no lateralizing neurologic findings. A lumbar puncture reveals no cells or organisms in the cerebrospinal fluid.

What Do You Think is Going on with This Patient?

The clinical presentation suggests neuroleptic malignant syndrome (NMS). Although first described more than 50 years ago, the diagnosis of NMS is primarily clinical (1).

What Key Findings Lead to the Diagnosis?

Clues to an NMS diagnosis include a recent diagnosis of a psychotic disorder and inpatient psychiatric hospitalization. This information, along with a careful medication history, would suggest that the patient has been recently, or is potentially, aggressive. He is started on an antipsychotic medication. Other important features include pyrexia, extrapyramidal symptoms such as rigidity, and an altered level of consciousness (2). The time course also provides important information in this case. NMS typically develops within 24 to 72 h after starting the offending medication (3). The majority of cases of NMS develop symptoms within the first week, and virtually all develop symptoms within the first 30 days (1). The type of antipsychotic may be less helpful for diagnosis. NMS is more common after high-potency, first-generation antipsychotics (FGAs) like haloperidol, although it

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Table 1. Medications Associated with Neuroleptic Malignant Syndrome

First-generation antipsychotics
Chlorpromazine
Fluphenazine
Haloperidol
Loxapine
Mesoridazine
Molindone
Perphenazine
Pimozide
Thioridazine
Thiothixene
Trifluoperazine
Second-generation antipsychotics
Aripiprazole
Clozapine
Olanzapine
Paliperidone
Quetiapine
Risperidone
Ziprasidone
Antiemetics
Domperidone
Droperidol
Metoclopramide
Prochlorperazine
Promethazine

can occur with any antipsychotic (Table 1) (4,5). There is some evidence, however, that NMS after SGAs may be less likely to present with rigidity (6).

The physical examination is also characteristic of classic NMS. Although cases of severe serotonin syndrome toxicity are difficult to distinguish from NMS, these cases usually have a history that involves ingestion of large quantities of serotonergic agents along with hyper-reflexia, which is characteristically more pronounced in the lower extremities. In this case, rigidity strongly suggests NMS. An elevated serum creatine kinase would also support this diagnosis, although rare cases of NMS without creatine kinase elevation have been reported (7).

Although many clinical definitions of NMS have been proposed, a recent international consensus study of NMS experts has proposed the definition shown in Table 2 (8). These guidelines confirm that NMS remains a clinical diagnosis. The final criterion proposed by the expert panel is having a negative work-up of other causes related to the primary symptoms. As there is no one particular laboratory value or imaging study that leads to diagnosis, a negative evaluation supports the diagnosis by ruling out mimickers.

What Other Diagnoses Should You Consider?

NMS is often difficult to distinguish from other causes of fever and altered mental status during the acute evaluation. The differential diagnosis of NMS can be broad and is included in Table 3.

Table 2. Diagnostic Criteria for Neuroleptic Malignant Syndrome

Recent dopamine antagonist exposure or dopamine agonist withdrawal
Hyperthermia, >100.4°F or >38.0°C on at least 2 occasions
Rigidity
Mental status alteration
Creatinine kinase elevation at least four times the upper limit of normal
Sympathetic nervous system lability: blood pressure elevation, $\geq 25\%$ above baseline; blood pressure fluctuation, ≥ 20 mm Hg (diastolic) or ≥ 25 mm Hg (systolic) change within 24 h
Tachycardia $\geq 25\%$ above baseline and tachypnea $\geq 50\%$ above baseline
Negative work-up for other causes (cerebrospinal fluid is characteristically normal)

As an Emergency Physician, What Do You Need to Know About NMS?

NMS is rare, with an estimated incidence of 0.02% to 3.23%, although some prospective studies have documented a far lower incidence of <1% (9–11). In part, this is because the main risk factor for NMS is usually exposure to a dopamine antagonist, although rarely it can occur after withdrawal of a dopamine agonist. NMS was more common with FGAs because they bind to dopamine receptors more avidly than second-generation antipsychotics (SGAs) (12). Table 1 contains a list of medications that have been associated with NMS. Consequently, with treatment moving toward less-frequent use of FGAs, NMS is now less common than in years past. Despite this, the mortality rate still remains high, at approximately 8% to 11.6%, and might actually be higher than in the era before SGAs (10,13). Another mortality risk factor appears to be premonitory dehydration, which is further exacerbated by the syndrome (14).

Table 3. Differential Diagnosis of Neuroleptic Malignant Syndrome

Anticholinergic poisoning
Dystonic reaction
Encephalitis
Excited catatonia
Excited delirium syndrome
Heat stroke
Malignant hyperthermia
Meningitis
Nonconvulsive status epilepticus
Pheochromocytoma
Porphyria
Rabies
Serotonin syndrome
Strychnine poisoning
Sympathomimetic intoxication, cocaine, methamphetamine, phencyclidine
Tetanus
Thyroid storm
Withdrawal from intrathecal baclofen

How Should You Stabilize This Patient?

- Airway management and circulatory support
- Intravenous benzodiazepines (15)
- Aggressive cooling measures
- Intravenous fluid hydration (rhabdomyolysis is common)
- Appropriate laboratory studies should include electrolytes, glucose, thyroid-stimulating hormone, creatine phosphokinase, urinalysis, and liver function tests
- Lumbar puncture is useful to exclude central nervous system infectious causes (3,10)
- Toxicology consultation
- Intensive care unit hospitalization
- Stop all dopamine antagonists, including first-generation antipsychotics, second-generation antipsychotics, or anti-emetics, such as metoclopramide
- Restart dopamine agonist (if NMS related to withdrawal)

Controversies in Treatment: What Are the Most Important Steps in the Management of This Patient?

Although the treatment of NMS is primarily supportive, multiple case reports have documented the successful use of dantrolene (16,17). Several reviews of the literature have also found encouraging results for the use of dantrolene, bromocriptine, and amantadine (18–20). Sakkas et al., for example, performed a case-control analysis on the effectiveness of dantrolene, bromocriptine, and amantadine for treating NMS based on reviewing all published studies (19). In control groups not treated with these medications, the NMS-related death rate was 21%. Dantrolene alone was reported to reduce the death rate to 8.6%, bromocriptine alone to 7.8%, and amantadine alone to 5.9%. The authors also stratified patients into five levels of severity based on the state of consciousness and temperature level, and reported that the relative reduction in death rate held up at all levels (19).

Rosenberg and Green reviewed the literature of 64 case reports of patients treated for NMS (20). They report the mean time to clinical response was 6.8 days when supportive measures were used alone. Dantrolene shortened the response time to 1.2 days and bromocriptine shortened the response time to 1.0 day; however, limitations in the study methods must be recognized.

Despite these findings, the evidence on the use of dantrolene is contradictory, and all recommend its use. There is no established dosing in NMS, but dantrolene is dosed at 2.5 mg/kg in malignant hyperthermia (21). Bromocriptine and amantadine are also used.

CLINICAL BOTTOM LINES

- The hallmark of NMS is recent exposure to dopamine agonists or recent withdrawal of dopamine antagonists, fever, rigidity, and altered mental status.
- For patients with probable NMS, provide aggressive supportive care with cooling and intravenous fluids and benzodiazepines.
- Toxicology consultation is prudent. The patient should be admitted to the intensive care unit.
- Stop all dopaminergic medications and avoid use of other medications with dopaminergic activity, such as metoclopramide, if possible.
- Dantrolene, bromocriptine, or amantadine is useful in severe cases.

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