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When a "Routine" Treatment for Agitation Causes Serious Harm: A Case of Rapid Onset Neuroleptic Malignant Syndrome

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Abstract

This case study is meant to educate medical personnel on how to recognize and manage neuroleptic malignant Syndrome (NMS), a serious adverse effect due to anti-psychotics and simultaneously highlighting this case as exceptionally rare given the rapidity of onset (<3 hours). We encourage providers to avoid reflexive orders for agitation/restlessness and consider other non-pharmacologic modalities and/or to adopt an initial reduced dosing strategy when appropriate. This case also assists to provide a better knowledge base regarding consequences of NMS and probable risk factors for developing this pathology. We describe a case of an 83-year-old female with a history of dementia who presented for behavioral changes according to her daughter. The patient underwent a recent long and appropriate tapering off of her opiates, which therefore negated any possibility of this being opiate withdrawal. Upon arrival she was quite agitated and subsequently received intravenous haloperidol. Following this, the patient developed an unusually rapid onset of rigidity, tachycardia, fever, and encephalopathy with laboratory findings revealing an elevated serum creatinine kinase. Her deteriorating status was reversed with the muscle relaxant, dantrolene, over the next 24 hours. Given her symptomatology and response to treatment, she was diagnosed with NMS.

Keywords: Neuroleptic malignant syndrome; NMS case; Anti-Psychotics; Agitation; Consequences; Risk factors

Introduction

Our case presentation below is meant to educate medical personnel on how to recognize and manage neuroleptic malignant Syndrome (NMS), a serious adverse effect to anti-psychotics. Also, we highlight this case as exceptionally rare given the rapidity of onset. We also use this case as a way to encourage providers to avoid reflexive orders for agitation/restlessness and consider other modalities or an initial reduced dosing strategy when appropriate. We attempt to better supplement providers' knowledge base regarding consequences of NMS and probable risk factors for developing this pathology.

Case Report

An 83-year-old female with a past medical history of chronic anemia, significant dementia, acid reflux, and osteoarthritis presents to the emergency room (ER) with behavioral changes at home. Her daughter provides the history and does mention her her outpatient doctor tapered the patient off of her chronic opiates for chronic arthritis over the time period of 7 months. The tapering was very slow and appropriate. Her last dose was 10 days prior to this presentation. At the time she stopped her opiates completely, she did develop diarrhea, suffered multiple falls, and was just not acting herself. This prompted the daughter to take her to another hospital for observation. Intravenous (IV) fluids were administered and the patient's symptoms resolved with only conservative management. Now present day, her daughter felt that her mother was showing signs of increased agitation/distress. The daughter described strewn belongings in the patient's room, which was unlike how the patient conducts herself. Her daughter thought her mother was in pain, possibly due to headache, abdominal pain or generalized arthritic pain as the patient was no longer on opiates. However, pinpointing the cause of her behavioral change proved difficult given her baseline dementia.

Upon presentation to the ER, the patient was found to be have an automated blood pressure of 200/120 mmhg, HR 90, RR 18, Temperature 36.5°C. She also appeared to be in an agitated state. She was very restless, uncooperative, and pulling at her IV line, presenting a danger to herself. A 2 mg dose of IV haloperidol was given to the patient as well as 10 mg IV labetalol.

Two-three hours later, the patient's vital signs and exam changed significantly. Blood pressure 190/90, HR 130, RR 24, Temperature 37.1°C. On exam she was in distress, encephalopathic, and could not follow commands. Her jaw was clenched. No JVD. No nystagmus. She was tachycardic with regular rhythm without murmur. She was tachypneic with clear lung sounds. Abdomen was soft without exhibiting a pain response. She had no extremity edema with pulses intact. Her fists were clenched, salivating, upper and lower extremities were severely rigid, pedal clonus was exhibited, but not spontaneous. Two consecutive doses of 1 mg benztropine were administered to treat possible extrapyramidal dystonic reaction secondary to haloperidol. The patient did not improve. Soon after the patient developed a fever of 40°C.

Initially, her lab values were within normal limits, except for a mild anemia, comparable to the patient's labs 2 months ago.

However, following the onset of fever, repeat labs revealed: (**Table 1**)

Laboratory test	Patients` value	Normal range
WBC	16,000 per ml	5,000-10,000 per ml
HGB	11.0 g/dl	12-16 g/dl
PLT	323,000 per ml	150,000-400,000 per ml
Na	133 mmol/L	136-145 mmol/L
K	4.2 mmol/L	3.5-5.0 mmol/L
Cl	96 mmol/L	98-106 mmol/L
HCO3	26 mmol/L	22-32 mmol/L
BUN	23 mg/dl	9-23 mg/dl
Cr	1.24 mg/dl	0.9-1.5 mg/dl
Creatinine Kinase (CK)	2,784 Intnl	10-80 Intnl
Troponin-I	4.81 ng/ml	<0.03 ng/ml
BNP	2,071 pg/ml	<100 pg/ml

Table 1 Onset of fever and Repeat labs

WBC: White Blood Cell, HGB: Hemoglobin, PLT: Platelets, Na: Sodium, K: Potassium, Cl: Chloride, HCO3: Bicarbonate, BUN: Blood Urea Nitrogen, Cr: Creatinine, CK: Creatinine Kinase, BNP: Beta Natriuretic Peptide

Chest Xray revealed clear lung fields. A Non-contrast head CT showed atrophy and small vessel ischemic disease without acute findings.

At this time, the most likely diagnosis was Neuroleptic Malignant Syndrome. The patient was started on dantrolene 40 mg IV every 6 hours for 4 doses. Within 24 hours, her rigidity had begun to improve and her CK declined by 40%. Unfortunately, as specified by her elevated troponin and EKG readings below, she did suffer an anterior wall ST elevation myocardial infarction as a complication of NMS.

Subtle elevated ST segment changes in **Figure 1**, evolving into further ST elevation on repeat EKG seen in **Figure 2** (20 minutes later).

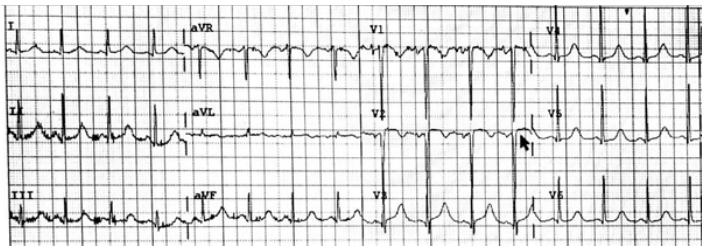

Figure 1 Subtle elevated ST segment changes

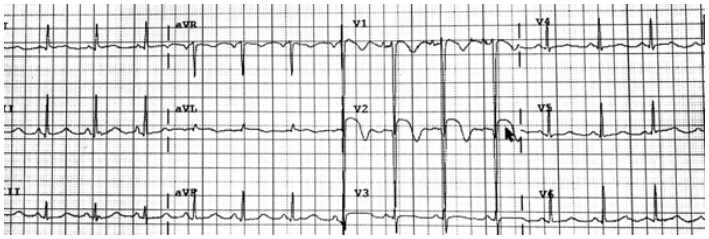

Figure 2 Further ST elevation on repeat EKG

An Echocardiogram confirmed anterior wall and anterior septal hypokinesis with an ejection fraction of 45%. Given her age and underlying dementia, her daughter decided to treat her conservatively rather than with percutaneous intervention. Her blood pressure improved once her agitation subsided. The patient continued to improve back to her baseline and was subsequently discharged to the care of her daughter.

Discussion

NMS can be a life-threatening adverse reaction due to antipsychotic medications. It is described more often with the use of the 1st generation antipsychotics such as Chlorpromazine, Fluphenazine or Haloperidol [1]. Over the past decade the incidence has dropped from about 1/500 to 1/5000 as new agents have been released less associated with NMS (i.e. second-generation antipsychotics) [2]. The time of onset following the offending drug is typically within 2 weeks. Our patient's onset of typical NMS symptoms began within 3 hours following administration of Haloperidol. Only 16% of NMS cases begin within one day of initiation of an antipsychotic [2]. The rapid onset observed in this case is far less common. After an extensive search of PubMed cases of NMS, a similar documented rapid onset of NMS was not found.

NMS is often suspected when the triad of muscle rigidity, fever, and altered mentation appears. Altered mentation can present as catatonia with akinesis and mutism similar to what was seen in our case [3]. However, not all patients will exhibit all three of these findings simultaneously.

Diagnosis of NMS is based on the following [4]:

- Severe Muscle rigidity and fever following use of an antipsychotic.
- Two (or more): Sweats, Difficulty Swallowing, Tremor,

Incontinence, Mutism, Tachycardia, Variable Blood Pressure, Leukocytosis, Delirium, Elevated Creatinine kinase.

- Symptoms cannot be attributed to another cause other than NMS (ie Sepsis, Seizure, etc)
- Symptoms cannot be explained by another psychiatric illness

Risk factors for developing NMS include the use of higher doses of antipsychotics, dehydration, and electrolyte disturbances. Alcohol/substance abuse and agitation have also been described. Agitation was certainly described in our patient upon presentation and the initial dose of haloperidol was certainly not a conservative one. Interestingly, age and gender has not been described to influence risk [3,5].

The differential diagnosis in this case was limited, although all important to consider. Differentials that should come to mind include severe anticholinergic reactions, acute dystonic reaction, meningoencephalitis/sepsis, thyrotoxicosis, serotonin syndrome, and malignant hyperthermia among others [6]. Our patient's reaction to haloperidol limited our differential diagnosis; although benztropine (anti-cholinergic) was administered initially as her first distinguishing features of NMS was severe rigidity and further altered mentation, which could have represented acute dystonia +/- an extrapyramidal adverse effect.

Treatment is mainly withdrawal of the offending medication. Following this, IV fluids are very important especially given fluid losses from hyperthermia and the risk of rhabdomyolysis-induced renal injury. Other means of dropping body temperature such as ice packs and cooling blankets can be utilized if needed as well. The provider should ensure that all electrolyte and metabolic derangements are corrected and followed closely [1]. These modalities were not enough for our patient. We utilized specific pharmacotherapy given the severity of the case and consequences that ensued. Both bromocriptine mesylate and dantrolene sodium are used most commonly. One is a dopamine agonist and the other a muscle relaxant, respectively. These medications can reduce the duration of symptoms, and one can propose they thereby reduce morbidity and mortality especially in those with known neurologic, renal, cardiac, and pulmonary comorbidities given NMS often leads to acute kidney failure, respiratory insufficiency, myocardial infarction, and toxic encephalopathy. Two of these complications were highlighted in our case (i.e. neuro and cardiac). The patient's blood pressure recovered quickly as her agitation and rigidity improved. There was no evidence of another cause of uncontrolled hypertension such as aortic dissection, stroke, or congestive heart failure to name a few [7]. Furthermore, such serious complications predict a poor prognosis. Therefore, prompt treatment should follow high suspicion for NMS and it is imperative to avoid increased morbidity and mortality. However, despite continued use of these medications, data has conflicted regarding their effectiveness [8].

Conclusion

Our case is unique given the rapid onset of NMS (under 3 hours). Although acute dystonia could explain the initial rigidity, the patient also was experiencing tachycardia and fever. As sepsis was ruled out, NMS was the most likely diagnosis. This case further expands the medical literature regarding the rapid onset of NMS, as most cases develop 24 hours or later.

Our case highlights the importance of considering all options to treat agitation and encourages providers to be aware of adverse effects. In our case, the patient was recently weaned from opiates, but given her dementia, she was unable to communicate chronic pain she may have been experiencing. This in combination of being in a new and noisy environment without the comfort of her daughter given COVID-19 visiting limitations was very challenging for her. Although Haldol may have been warranted in this case, starting low and titrating slow would have been wise. (i.e. 0.5 mg Haldol IV to start).

Finally, our case highlights the importance of controlling the autonomic symptoms of NMS as severe complications can develop such as myocardial infarction, especially in fragile populations as is the patient in our case.

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Nil.

Conflict of Interest

There are no conflicts of interest.

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