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Neuroleptic Malignant Syndrome: Catch Me If You Can; A Case Report

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is a relatively rare adverse reaction to neuroleptic medications. It is characterized by a constellation of findings that usually occur concurrently. These include vital instability, fever, elevated creatinine kinase, encephalopathy, and muscle rigidity. Having a high index of suspicion can reduce mortality and long-term complications by having a broad differential diagnosis when facing a patient with these symptoms, particularly if they are on antipsychotic medications. Withdrawal of the offending medication and supportive therapy are the most important initial steps in patient management.
In this case report, we discuss the case of a 95-year-old male on quetiapine and memantine with a 2-day history of fever, rigidity, cough, and reduced activity after increasing the dose of quetiapine three days prior to his presentation.

Key Words: Neuroleptic malignant syndrome, Antipsychotics, Neuroleptics, Muscle rigidity Creatinine Kinase

INTRODUCTION

NMS is a rare but potentially lethal condition that requires prompt recognition and stabilization. It occurs as a side effect of using dopamine-receptor antagonist medications or due to the rapid withdrawal of dopaminergic medications. [(1)] Studies show that the incidence of NMS is around 3% or less in patients taking conventional antipsychotic medications. [(2-4)]

Patients with NMS commonly present with fever, muscle rigidity, altered consciousness level, and autonomic dysregulation. [(5)] Given this wide array of clinical presentations, the most challenging aspect of NMS remains the early recognition of the condition. Such clinical pictures can be misleading as they present similar clinical pictures to more commonly known disorders. Thus, healthcare professionals should always have a high level of suspicion and awareness, especially if a patient is on antipsychotic medications. Here, we describe a case of NMS in an elderly patient that was diagnosed in a timely manner and managed successfully.

CASE PRESENTATION

A 95-year-old male with Alzheimer's disease on quetiapine and memantine was brought by ambulance from a geriatric home with a 2-day history of fever, productive cough, reduced activity, and poor feeding. The patient had no history of sick contact and received two doses of the Sinopharm vaccine. The latest dose was in July 2021.

Prior to arrival at the emergency room, the patient's fever reached 38.7 C and

his oxygen (O2) saturation dropped to 89% on room air. Hence, he was given paracetamol and kept on a face mask with 4 L of oxygen.

On arrival, the patient's temperature was reduced to 37.5 °C, O2 saturation was 96% on room air, blood pressure was 114/85 mmHg, pulse was 122/min with a low body mass index (around 18 kg/m2). On examination, the patient was bedridden, alert and conscious with masked face and mutism. The pupillary reflex was intact and meningeal signs could not be assessed as the patient had overall body stiffness and was resisting examination. Initially patient had hypertonia in the left arm, but normal tone in the right arm, with flexed bilateral lower. Reflexes could not be elicited. Babinski's sign was negative and gait could not be assessed. Abdomen was soft with no tenderness. A urine catheter was placed in place. Chest and cardiac examinations were unremarkable. Cardiac monitor showed sinus tachycardia with occasional PVC.

Our initial impressions based on the limited history and initial examination, were as follow: COVID-19, aspiration pneumonia, meningitis, with or without UTI or electrolyte imbalance due to his recent history of reduce oral intake.

Initial laboratory findings included hemoglobin of 11.6 gm/dL, white blood cell count of 8.8*1012/L with a neutrophil shift of 77.4%, platelet count of 247*109/L, urea of 9.8 mmol/l, creatinine of 80 MUmol/l, electrolytes, and liver function tests that were unremarkable. Initial troponin I of 1.300 ng/ml, creatinine kinase (CK), ran as high as 1301 U/L.

Urine analysis showed RBC more than 100, with 3+ blood hemoglobin, but negative nitrate and no rise in urine WBC. Chest x-ray was unremarkable, COVID-19 antigen and PCR were negative.

We re-examined the patient and interestingly, his both arms became flexed resistance to examination with lead pipe rigidity movement. His abdomen became rigid with orange discoloration of the urine. Clonus was negative. At this time the cardiac monitor showed query flutter waves. An ECG was taken and it shows many artifacts as if the patient was moving or had muscular fasciculation.

Here, we assumed that patient might developed NMS as he is on antipsychotics and presented with fever, muscle rigidity and mutism with tachycardia and dark urine which alerted towards muscle breakdown, renal failure with suspicion of early rhabdomyolysis. The absence of clonus reduced the possibility of serotonin syndrome which shares similar features with NMS. Hence, we re-contacted the assigned staff who brought the patient regarding patient's medications for more information, as no documented data was seen in the previous records. The staff said that three days before admission, the patient's quetiapine dose was increased from 25mg to 50mg HS, where his memantine dose was kept at the same level 20mg OD.

We believed that patient is having NMS and was kept on IV fluids for proper hydration with a strict input/output chart and his regular medications (quetiapine and memantine) were discontinued. However, a stat dose of 5 mg of diazepam was given to control the rigidity and we called the medical on-call to review the patient.

The medical on-call doctor came to assess the patient and asked for surgical referral as the patient had a rigid abdomen, but we reminded him with NMS signs and symptoms which usually include overall muscle rigidity and was told to consult the surgical team if he thinks that perforated viscous is the most likely diagnosis. Then he wanted the patient to be admitted under neurology as NMS by its name suggest a neurological problem. We explained to him that the need of being admitted under medical care and force admission was done under medical department.

After 24 hours, repeated labs showed troponin I of 0.89 ng/ml, creatinine kinase of 991 U/l and the following day, troponin I and CK decreased to 0.620 ng/ml and 764 ng/ml, respectively. On the 4th day, further reduction of troponin and CK was noted

(0.14 ng/ml and CK 310, respectively). In addition, the LDH level remained within the normal limit throughout his admission. As well, repeated urine test showed the same initial result.

During patient admission, the psychiatry team reviewed the patient and advised to discontinue quetiapine and to continue follow up with the community psychiatry service.

Upon discharge, patient was vitally stable and afebrile, was oriented to person and place, and was not agitated; the stiffness had significantly decreased.

DISCUSSION

Epidemiology

In 1967, NMS was previously known as "akinetic hypertonic syndrome". [(6)] It is the most serious adverse effect of neuroleptic medications. Although it has a low incidence rate, it can be a cause of significant morbidity and mortality. reports estimated mortality rates to range between 5.6% and 12%. [(7, 8)]

NMS is associated mostly with the male gender and can affect individuals from different age groups, particularly younger adults. This can be related to the likelihood of usage of antipsychotic medications. [(9,10)]

Pathophysiology

NMS pathophysiology remains controversial, with different theories being raised. Many authors believe that it arises as a consequence of blocking dopaminergic receptors in the hypothalamus, nigrostriatal track, mesolimbic or cortical pathways. Especially with the use of high-potency neuroleptic medications that strongly affect the D2 receptor (such as haloperidol). [(9-12)]

This theory is based on several evidence: as NMS frequently was seen after the initiation or changing the dose of dopaminergic medications or even after the rapid discontinuation of these drugs, central dopamine tract lesions resulted in symptoms similar to NMS characteristics, and finally dopaminergic medications can benefit patients with NMS. [(11)]

Other theories suggest that NMS shares the same pathophysiology as malignant hypertension, that sympathoadrenal dysfunction might have a role in developing NMS, and that low serum iron levels can reduce dopaminergic receptors and thus increase the likelihood of NMS. [(1)] Predispositions to developing NMS may include dehydration, infection, trauma, recent surgery or being pregnant. Also, genetics has a contributory role in developing NMS. [(9)]

In table 1, we listed different medications that can result in NMS, including typical and atypical neuroleptic medications, anti-emetics, and others.

Table 1 shows the medications that have been linked to an increased risk of NMS.

Typical Neuroleptics	Atypical Neuroleptics	Anti-emetics	Others
Haloperidol	Olanzapine	Droperidol	Levodopa
Chlorpromazine	Clozapine	Domperidone	Amantadine
Fluphenazine	Risperidone	Metoclopramide	Tetrabenazine
Thioridazine	Quetiapine	Promethazine	Reserpine
Trifluordazine	Ziprasidone	Prochlorperazine	Amoxapine
Thiothixene	Aripiprazole		Diatrizoate
Loxapine	Zotepine		Lithium
Bromperidol	Amisulpride		Phenelzine
Promazine			Dosulepin
Clopenthixol			

Our patient exhibited two factors: the first and most important one is that he had a recent increase in quetiapine dose, which is not uncommon to play a role in developing NMS. [(13)] The second possible factor is that our patient might have had some degree of dehydration as he is living in a geriatric home.

Diagnosis

To diagnose NMS, doctors should rule out other differential diagnosis that

share similar clinical presentation and these include but not limited to central nervous system infections, sepsis, lithium toxicity, extrapyramidal side effects, thyrotoxicosis, heatstroke, serotonin syndrome and malignant hyperthermia. [(1)]

No definitive universal diagnostic criteria are used to diagnose NMS. However, different authors reported several diagnostic criteria that share similar features, such as the American Psychiatric Association Diagnostic and Statistics Manual of Mental Disorders (DSM-IV), the World Health Organization International Classification of Diseases 10th revision (ICD-10), and Levenson's criteria. [(14)]

We used the DSM-IV diagnostic criteria illustrated in table 2 to diagnose NMS in our patient. He meets the three major criteria and three of the minor criteria: mutism, tachycardia, and elevated creatinine phosphokinase, and could not be explained by another differential.

Major Criteria (all must be met)	**Other criteria (at least two required)**
Exposure to dopamine-blocking agents Severe muscle rigidity Fever	Diaphoresis Dysphagia Tremor Incontinence Altered level of consciousness Mutism Tachycardia Elevated or labile blood pressure Leukocytosis Elevated creatine phosphokinase
C. The symptoms in criteria A+ B are not due to another substance or neurological or other medical condition. D. The symptoms in criteria A+B are not better accounted for mental disorder	

Management

Regarding treatment of NMS, early recognition and stopping the causative agent are the key factors for successful management. Nevertheless, supportive therapy is the mainstay of NMS, and this includes hydration, correcting electrolyte disturbance, restoring body temperature, providing venous thromboembolism prophylaxis, lowering elevated blood pressure, and preventing further complications. [(1)]

In our case, due to the limited history and initial normal examination we thought of other common differential diagnosis, but then based on the labs, repeated physical examination and link to the fact that he is on antipsychotic, we believed that NMS is the most likely diagnosis, supportive therapy alone was adequate in managing his condition and reducing the CK. However, we believe that physicians' awareness about rare but fetal conditions that they might encounter especially during busy on-calls is by far the most important step. And as evident by the literature, in extreme cases where NMS patients have a high grade of fever and rigidity, Dantrolene may exhibit some benefit as it is considered a muscle relaxant. [(11)]

The typical dose of Dantrolene is 2 mg/kg and is repeated every 10 minutes if required. However, adverse effects such as hepatotoxicity and respiratory depression have been reported, especially when the dosage exceeds 10 mg/kg over 24 hours. [(1,11)] As evidenced by some case reports, ECT has been shown to be effective in resistant cases where medical therapy has failed. [(11, 15)]

To prevent a recurrence of NMS, managing possible risk factors such as dehydration and electrolyte imbalance is important. Additionally, medication review should be done regularly to consider the need for discontinuation of unnecessary medications. For example, our patient was on quetiapine for Alzheimer's disease. Although it has been reported in the literature that quetiapine has a modest impact on improving agitation, it appears to be associated with cognitive decline. [(16)] Hence, should started on different medication for Alzheimer's disease.

Complications

NMS can result in several complications besides death, such as rhabdomyolysis, acute renal failure, acute respiratory distress, and arrhythmia. [(17)] Also, survivors may still experience permanent neurological deficits, including ataxia and dyskinesia. [(17)]

In our case, we think that our patient experienced some degree of muscle injury as he had dark urine with hemoglobinuria and a high CK level, but he did not develop rhabdomyolysis as the CK level was not 5 times the upper normal limit and he did not have renal impairment or any electrolyte disturbance, which is usually seen in rhabdomyolysis. [(18)]

CONCLUSION

NMS is a challenging diagnosis, which can be fetal if not managed quickly, and Prompt withdrawal of the offending agent is by far the most important initial step. Supportive therapy in some cases can be sufficient, where specific treatments may be used in severe cases. Finally, we would like to emphasise the importance of regular psychiatry follows up for patients on antipsychotic medications, particularly those in geriatric home as many of them would be elderly and cannot express their symptoms properly.

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