

## CLINICAL VIGNETTE

# An Interesting Presentation of Neuroleptic Malignant Syndrome

Amar C. Nawathe, MD and Michael E. Lazarus, MD

A 63-year-old man, a resident of board and care facility, was brought to the emergency room with one-day history of increasing lethargy. He was hypotensive (75/47 mm Hg), tachycardic (130 beats/minute) and febrile (101.4 °Fahrenheit). Blood work exhibited leukocytosis of 16,400 per microliter, renal failure with blood urea nitrogen of 34 mg/dL and serum creatinine of 1.6 mg/dL, troponin of 4.3 ng/mL, and creatine kinase of 6799 U/L and mild transaminitis. Venous lactate was 4.9 mmol/L and serum procalcitonin was elevated 20 ng/mL. 12-lead ECG revealed sinus tachycardia without ST segment or T wave changes. His past medical history was significant for diabetes mellitus and schizophrenia. His medication list included ascorbic acid, benzotropine, clonazepam, deutetrabenazine, divalproex, adult multivitamins, quetiapine, ropinirole, and venlafaxine. On physical exam, he was confused, exhibited generalized extremity stiffness, with voluntary movements and tremors. He denied chest pain but was not able to provide any other medical information. No further medical history could be obtained either from the board and care staff or his family. A non-contrast Computed Tomographic (CT) scan of his head did not show any acute findings. Initially, his working diagnosis was sepsis. A CT scan of the chest, abdomen and pelvis did not show any obvious source of infection. Blood cultures were drawn and he began empiric antibiotic therapy and given aggressive intravenous fluids. Due to concern for a silent myocardial infarction with underlying diabetes mellitus, an echocardiogram performed in the emergency room, revealed a normal left ventricular function without wall motion abnormalities.

On hospital day 2, his clinical findings were significant for rising creatine kinase, procalcitonin and transaminase levels. Contact with his mother was established, who informed us that the patient was having “Parkinson-type side effects” from his psychiatric medications, and he was initiated on deutetrabenazine a month prior with a subsequent dose increase by his neurologist. Neurology inpatient consultation was requested and a diagnosis of Neuroleptic Malignant Syndrome was made and Deutetrabenazine, quetiapine, divalproex and venlafaxine were discontinued. Our patient was started on bromocriptine with continued aggressive intravenous hydration. His clinical condition stabilized over the next few days and he was discharged home on hospital day 6 in stable condition.

### Discussion

Neuroleptic malignant syndrome (NMS) was first described in 1956 shortly after the introduction of chlorpromazine. How-

ever, in 1960, French investigators, Delay and colleagues named it as “syndrome malin des neuroleptics” as an adverse effect to newly introduced haloperidol, translated into English as Neuroleptic malignant syndrome.<sup>1</sup> The Diagnostic and statistical manual-5 of the American Psychiatric Association lists the diagnostic features for NMS as hyperthermia [temperature > 100°F or >38°C measured orally] on two occasions with diaphoresis; generalized rigidity unresponsive to antiparkinsonian medications; change in mentation with delirium or altered level of consciousness from stupor to coma; and autonomic dysfunction manifested by tachycardia (rate >25% above baseline), diaphoresis, blood pressure elevation (systolic or diastolic >25% above baseline) or fluctuation (>20 mmHg diastolic change or >25 mmHg systolic change within 24 hours), urinary incontinence, and pallor. Creatine kinase elevation of at least four times the upper limit of normal is commonly seen. Tachypnea (rate >50% above baseline) is also encountered frequently, and respiratory distress—resulting from metabolic acidosis, hypermetabolism, chest wall restriction, aspiration pneumonia, or pulmonary emboli—can occur and lead to sudden respiratory arrest.<sup>2</sup>

Patients taking typical antipsychotics are at the highest risk of developing NMS. However, NMS has been reported as an adverse effect of most atypical antipsychotics, non-neuroleptics with anti-dopaminergic activity such as metoclopramide, and other agents such as lithium. Abrupt withdrawal of dopaminergic agents such as levodopa has also resulted in NMS. Pathophysiologic mechanisms of NMS are still not completely understood, but sudden central dopaminergic depletion resulting from dopaminergic-2 (D-2) receptor blockade plays a major role. D-2 receptor blockade in the nigrostriatal, hypothalamic and mesolimbic/cortical pathways can respectively explain rigidity, hyperthermia and altered mentation in NMS. Since not all the symptoms of NMS are explained by the above mechanism and drugs without anti-dopaminergic activity can precipitate NMS, alternative mechanisms have been proposed. Sympatho-adrenal hyperactivity from removal of tonic inhibition from within the sympathetic nervous system may play a role. Also proposed is a defect in the calcium regulatory proteins in the sympathetic neurons possibly sharing a mechanism similar to malignant hyperthermia. Another mechanism suggested is in the skeletal muscles with an increase in calcium release in the sarcoplasmic reticulum from antipsychotic use, resulting in increased muscle contractility and rigidity, muscle breakdown and hyperthermia.<sup>1</sup>

Two factors in NMS precipitation are likely in this case. First, the recent introduction of deutetrabenazine for treatment of his tardive dyskinesia a month prior and an increase in drug dose prior to his presentation; second, a possible additive effect of further dopamine suppression from his other psychiatric medications; quetiapine and venlafaxine. Deutetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor receiving FDA approval in 2017 for treatment of chorea associated with Huntington's disease.<sup>3</sup> It can be used to treat tardive dyskinesia, as in our patient. VMAT2 sequesters dopamine in presynaptic vesicles. Upon fusion of the vesicle with the presynaptic membrane, dopamine is released into the synaptic cleft to interact with postsynaptic dopamine receptors. VMAT2 inhibitors block vesicular storage of dopamine and thus deplete its receptor availability.<sup>4</sup>

Clinical features of NMS share similarities with several other clinical entities. More common scenarios are infections including those of the central nervous system, sepsis and drug intoxications, which require an upfront thorough assessment. Heat stroke and serotonin syndrome should be considered. Heatstroke presents with hyperthermia but in contrast to NMS is associated with a dry skin and loss of muscle tone. Serotonin syndrome manifests with altered mentation and autonomic dysfunction like NMS, but in contrast, has symptoms of gastrointestinal hypermotility, lack of leukocytosis or creatine kinase elevation, presence of hyperreflexia, myoclonus and antecedent polypharmacy including selective serotonin release uptake inhibitors. Malignant hyperthermia presents similarly to NMS but has an exposure history to an inhaled anesthetic or depolarizing muscle relaxant that helps differentiate the diagnosis. Lastly, it is important to mention that lethal catatonia is similar in presentation to NMS. Second generation antipsychotics are used in management of the former and possible offending agents and contraindicated in the latter.<sup>1,5</sup> Differentiating between the two becomes critical and expert neuropsychiatry consultation is recommended.

The onset of symptoms of NMS varies from hours to days after the offending drug initiation. Some cases develop within 24 hours after drug initiation, most within the first week, and virtually all cases within 30 days.<sup>2</sup> In our patient, our initial evaluation was hindered by lack of knowledge of the duration of his multiple psychiatric medications. Presenting during a winter month and with risk of infectious exposures from his board and care facility, sepsis syndrome was suspected and its time sensitive treatment had to be initiated. Significant elevation of procalcitonin also supported the initial working diagnosis of bacterial infection and sepsis. Procalcitonin elevation however has been reported in NMS in absence of a bacterial infection.<sup>6</sup> Microbiology work up in our patient was negative and his antibiotics were discontinued.

Treatment of NMS requires stopping the offending agent, or reinitiation of the dopaminergic agent, if the syndrome is precipitated by abrupt withdrawal of the latter. Fluid hydration, correction of rhabdomyolysis, supportive care for other organ involvement, and in severe cases, an intensive care unit

admission maybe needed. In cases not responding to initial care, empiric pharmacologic therapy is recommended. Dopamine agonist, bromocriptine works by reversing the hypodopaminergic state. Dantrolene sodium, a muscle relaxant, works by blocking calcium release in the sarcoplasmic reticulum. Combining the two agents has not been shown to be beneficial over using them individually. Dantrolene being hepatotoxic is generally stopped as NMS resolves, whereas bromocriptine is continued for at least 10 days when the offending agent was taken orally and 2-3 weeks if the offending agent was a depot preparation. In cases that do not respond to medical therapy, electroconvulsive therapy has been shown to be effective.<sup>1</sup>

Based on the 2013 Medical Expenditure Panel Survey, 1.6 % of the U.S. population uses prescription antipsychotic medications.<sup>7</sup> Incidence rate for NMS is about 0.01%-0.02% among individuals treated with antipsychotics.<sup>2</sup> This is far less when compared to more common diseases with similar presentation in our daily practice. The CDC reports more than 1.5 million cases of sepsis per year and 1.1 million emergency room visits for drug overdose per year.<sup>8,9</sup> Nonetheless, missing the diagnosis of NMS can be fatal, and mortality from cardio-respiratory failure, pulmonary embolism renal failure, or disseminated intravascular coagulation is likely from delayed or lack of correct diagnosis. With increasing physician awareness however, NMS mortality has reduced from 30% to 10% over the last several decades. However, with prompt diagnosis and management, NMS holds a favorable prognosis with expected recovery within 2 weeks.<sup>1</sup>

## REFERENCES

1. **Berman BD.** Neuroleptic malignant syndrome: a review for neurohospitalists. *Neurohospitalist*. 2011 Jan;1(1):41-7. doi: 10.1177/1941875210386491. PubMed PMID: 23983836; PubMed Central PMCID: PMC3726098.
2. **American Psychiatric Association:** Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
3. Austedo (deutetrabenazine) [package insert]. Teva Pharmaceuticals USA, Inc. North Wales, PA 19454; 2017.
4. **Nieman N, Jankovic J.** Treatment of Tardive Dyskinesia: A General Overview with Focus on the Vesicular Monoamine Transporter 2 Inhibitors. *Drugs*. 2018. <https://doi.org/10.1007/s40265-018-0874-x>
5. **Velamoor R.** Neuroleptic malignant syndrome: A neuropsychiatric emergency: Recognition, prevention, and management. *Asian J Psychiatr*. 2017 Oct;29:106-109. doi: 10.1016/j.ajp.2017.05.004. Epub 2017 May 4. Review. PubMed PMID: 29061403.
6. **Cabot B, Pautas E, Gatey M, Perivier S, Mahieux F, Pinquier C, Hausfater P.** [Increase of serum procalcitonin levels during a neuroleptic malignant syndrome]. *Ann Biol Clin (Paris)*. 2009 Nov-Dec;67(6):697-700. doi: 10.1684/abc.2009.0383. French. PubMed PMID: 19939773.
7. **Moore TJ, Mattison DR.** Adult Utilization of Psychiatric Drugs and Differences by Sex, Age, and Race. *JAMA*

*Intern Med.* 2017 Feb 1;177(2):274-275. doi:10.1001/jamainternmed.2016.7507. PubMed PMID: 27942726.

8. Centers for Disease Control and Prevention. Protect your Patients from Sepsis. [https://www.cdc.gov/sepsis/pdfs/HCP\\_infographic\\_protect-your-patients-from-sepsis\\_508.pdf](https://www.cdc.gov/sepsis/pdfs/HCP_infographic_protect-your-patients-from-sepsis_508.pdf)
9. **Albert M, McCaig L, Uddin S.** Emergency department visits for drug poisoning: United States, 2008–2011. *NCHS data brief, no 196*. Hyattsville, MD: National Center for Health Statistics. 2015

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