Accepted Manuscript online: 2024-10-14 Article published online: 2024-11-12



# Neuroleptic Malignant Syndrome in a 10-Month-Old Ex-Preterm Infant with Delirium

Gloria Akuamoah-Boateng, MBChB[1] Kayla A. Buttafuoco[2] Courtney C. Sutton, PharmD[3] Brian P. Hackett, MD[4]

[1] Department of Pediatrics-Division of Neonatology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee
[2] Vanderbilt University School of Medicine, Nashville, Tennessee
[3] Department of Pharmacy-Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee
[4] Division of Neonatology, Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee

**Address for correspondence** Gloria Akuamoah-Boateng, MBChB, Monroe Carell Jr. Children's Hospital at Vanderbilt, 2200 Children's Way, Nashville, TN 37232 (e-mail: Gloria.akuamoah-boateng@vumc.org).

AJP Rep 2024;14:e259–e261.

## Abstract

In recent times, atypical antipsychotics are increasingly being used in the neonatal intensive care unit (NICU) for the management of neonatal delirium. As the recognition of delirium in NICU infants increases, caution should be exercised with use of antipsychotics for management, given associated adverse effects. Neuroleptic malignant syndrome (NMS) is a rare adverse drug reaction associated with exposure to antipsychotics and other antidopaminergic medications. Most reported cases of NMS in pediatric patients have been in older children on antipsychotic medications. We present a case of a 10-month-old former preterm infant who developed clinical signs suggestive of NMS after exposure to olanzapine for treatment of delirium. Our case report details the clinical course of this infant, delves into the condition, and outlines some useful lessons for the clinician in the identification and management of this rare but life-threatening adverse effect.

**Keywords**
- hyperthermia
- neuroleptic malignant syndrome
- delirium
- antipsychotics

## Key Points

- NMS is a rare side effect of antipsychotic medications.
- Hyperthermia with mental status changes could be due to NMS.
- Antipsychotics should be used cautiously in infants.

## Case Presentation

A 10-month-old, former 34-week, 6-day preterm infant with esophageal atresia, bronchogastric fistula, and right lower lobe pulmonary sequestration with a large aortopulmonary collateral underwent multiple surgeries requiring a prolonged course of postoperative sedating medications. He was started on olanzapine due to concern for delirium. Thirty-three days after initial exposure to olanzapine, he developed persistent agitation unresponsive to multiple PRN medications including acetaminophen, lorazepam, morphine, midazolam, and olanzapine. He subsequently developed decompensated shock and became obtunded. He was tachycardic to the 250s and hyperthermic with a peak rectal

**received**
December 15, 2023
**accepted after revision**
August 12, 2024
**accepted manuscript online**
October 14, 2024

**DOI** https://doi.org/10.1055/a-2441-4217.
**ISSN** 2157-6998.

© 2024. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/)

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

temperature of 42.9°C. Examination was significant for intermittent, nonsuppressible clonic movements in the extremities and intermittent upper extremity hypertonia. Fluid resuscitation and pressor support was initiated. The hypotension resolved with subsequent development of hypertension significant enough to be treated with nicardipine. A sepsis evaluation was performed, and broad-spectrum antibiotics were started. With persistent hyperthermia, not responsive to acetaminophen, active cooling was started.

Laboratory evaluation was notable for leukocytosis, a normal C-reactive protein, lactic acidosis, transaminitis, and acute kidney injury (AKI). Electrocardiogram showed sinus tachycardia. Echocardiography and chest X-ray were unremarkable. Electroencephalogram (EEG) showed left periodic discharges concerning cerebral irritation but no seizures. Initial creatine phosphokinase (CPK) was normal at 99 IU/L but increased to 4,962 IU/L within 24 hours and peaked at 5,585 IU/L. He subsequently developed multiorgan failure with disseminating intravascular coagulopathy, transaminitis, and worsening AKI.

Due to concern for neuroleptic malignant syndrome (NMS), olanzapine was stopped on the day of acute decompensation, and bromocriptine was initiated at 0.625 mg/d, which was later increased to 1.25 mg/d. A computed tomography (CT) scan of the brain showed no evidence of herniation or other acute processes. Brain magnetic resonance imaging (MRI) demonstrated subacute global anoxic injury, leptomeningeal enhancement, and parenchymal loss. He progressively deteriorated with anasarca, anuria, pulmonary edema with ensuing refractory hypoxia, and acidosis over the next 48 hours. Given his grim prognosis, care was redirected, and he died shortly after.

Autopsy was significant for acute and subacute myocardial infarction involving the interventricular septum, free walls of both ventricles, and papillary muscles. Neuropathology showed hypoxic-ischemic injury of the cerebral cortex, hippocampus, and deep gray matter, acute and subacute infarctions in the watershed regions of the left frontal lobe and periventricular white matter. Notably, there was no evidence of meningitis or cerebritis.

Based on the patient's clinical course including: (1) treatment with an atypical neuroleptic, (2) sustained fever $>40$°C not responsive to antipyretics, (3) intermittent muscle rigidity, (4) change in level on consciousness, (3) labile blood pressure (hypotension progressing to hypertension, (4) CPK $>1{,}000$ IU/L, (5) leukocytosis, and (6) tachycardia, a diagnosis of NMS was made. A diagnosis of sepsis and/or meningitis was also entertained and felt to be unlikely. Blood and urine cultures were negative and, although a lumbar puncture was not performed due to the patient's unstable condition, no evidence of meningitis was identified at the time of autopsy. CT scan of the head and MRI excluded any acute intracranial pathology to explain the patient's clinical course. The patient's other clinical and autopsy findings, such as cerebral edema, AKI, anasarca, and myocardial infarction are likely secondary to the patient's prolonged and complicated hospital course, as well as more acute end organ injury secondary to NMS.

## Discussion

NMS, is a rare idiosyncratic drug reaction typically characterized by a clinical tetrad of fever, altered mental status, muscle rigidity, and dysautonomia. It occurs after exposure to neuroleptics and other medications, which affect central dopaminergic neurotransmission.[1] Hypothalamic dopaminergic blockade is believed to be fundamental to the pathogenesis of NMS.[2,3] Alterations in the levels of other neurotransmitters such as gamma-aminobutyric acid, serotonin, and acetylcholine have also been implicated.[4] Serotonin syndrome and malignant hyperthermia have overlapping presentations with NMS but are associated with exposure to serotonergic medications and inhaled anesthetics, respectively.

Most reported cases of NMS in pediatric patients have been in older children on antipsychotic medications.[3] Few cases of NMS in infants have been reported following exposure to domperidone, risperidone, and methylphenidate.[5–7] Atypical antipsychotics, however, are increasingly being used in the neonatal intensive care unit (NICU) for the management of neonatal delirium.[8]

Symptom onset varies after exposure to the offending drug, ranging from 24 hours to 30 days.[5,6] Our patient developed symptoms 33 days following initial exposure to olanzapine, which although atypical, was in conjunction with receiving PRN olanzapine. Additionally, there are case reports of symptom onset greater than 30 days after the initiation of medication, particularly with a change in dose.[5,9,10] Although NMS typically presents with sustained muscle rigidity, our patient is presented with intermittent muscle rigidity of the upper extremities and clonus. Mild or absent muscle rigidity has been reported.[6,8] The finding of acute and subacute infarcts in the myocardium was also atypical, as NMS primarily affects skeletal muscles.[11,12] A case of a patient with NMS developing reversible Takotsubo cardiomyopathy mimicking a myocardial infarction has been reported.[13] Our patient's myocardial infarction was likely secondary to ischemia from NMS-related autonomic instability.[14,15]

Common laboratory findings include elevated CPK, leukocytosis, acidosis, and AKI. A CPK level greater than 1,000 IU/L is specific to NMS, with the degree of elevation correlating with disease severity and prognosis.[16,17] Our patient had markedly elevated CPK levels peaking at $>5{,}000$ IU/L. Neuroimaging is typically normal, but there have been reported findings of cerebral edema. Our patient's MRI showed marked cerebral edema consistent with subacute global anoxic injury, leptomeningeal enhancement, and parenchymal loss. There was not, however, a previous MRI for comparison so the timing of some findings may have predated the NMS and reflect chronic injury in a patient with a prolonged, complicated NICU course. EEG may show nonspecific generalized slow wave activity, consistent with our patient's EEG.[6]

Management is supportive and most importantly, stopping the causative agent. Other measures include active cooling, fluid resuscitation, urine alkalinization, blood

pressure support, deep vein thrombosis prophylaxis and use of benzodiazepines. In severe cases, specific therapy with muscle relaxants such as dantrolene or dopaminergic agents such as amantadine or bromocriptine can be considered.[6,16,18] We chose bromocriptine due to the absence of sustained muscle rigidity, the presence of acute liver dysfunction, and reports of shorter duration of illness with its use.[6]

Most patients have complete recovery within 2 weeks without neurologic sequelae.[18] Mortality rate is between 5 and 25% and is usually due to effects of dysautonomia and multiorgan dysfunction.[17,19] Of note, described outcomes are generally for older patients and outcome data for infants are very limited.

## Conclusion

As recognition of delirium in NICU infants increases, caution should be exercised with the use of antipsychotics as treatment options. Alterations in the mental status of an infant with preexisting delirium on antipsychotics, especially in association with hyperthermia, could be an early clue for NMS. Prompt recognition and management can improve outcomes.

**Conflict of Interest**
None declared.

## References

1 Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. Neurohospitalist 2011;1(01):41–47
2 Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? Neurology 1981;31(02):132–137
3 Kimura G, Kadoyama K, Brown JB, et al. Antipsychotics-associated serious adverse events in children: an analysis of the FAERS database. Int J Med Sci 2015;12(02):135–140
4 van Rensburg R, Decloedt EH. An approach to the pharmacotherapy of neuroleptic malignant syndrome. Psychopharmacol Bull 2019;49(01):84–91
5 Croarkin PE, Emslie GJ, Mayes TL. Neuroleptic malignant syndrome associated with atypical antipsychotics in pediatric patients: a review of published cases. J Clin Psychiatry 2008;69 (07):1157–1165
6 Neuhut R, Lindenmayer JP, Silva R. Neuroleptic malignant syndrome in children and adolescents on atypical antipsychotic medication: a review. J Child Adolesc Psychopharmacol 2009; 19(04):415–422
7 Penugonda AJ, Singh Y, Kattula D, Bhaskar M. Neuroleptic malignant syndrome in a 15-month-old child: a case report. J Clin Psychopharmacol 2023;43(05):455–456
8 Carbone JR. The neuroleptic malignant and serotonin syndromes. Emerg Med Clin North Am 2000;18(02):317–325, x
9 Kunz M, Gomes FA, Tramontina JF, Kapczinski F. Late-onset neuroleptic malignant syndrome in a patient using olanzapine. J Clin Psychopharmacol 2007;27(03):303–304
10 Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007;164(06):870–876
11 Kubo S, Orihara Y, Kitamura O, Ikematsu K, Tsuda R, Nakasono I. An autopsy case of neuroleptic malignant syndrome (NMS) and its immunohistochemical findings of muscle-associated proteins and mitochondria. Forensic Sci Int 2001;115(1–2):155–158
12 Keck PE Jr, Caroff SN, McElroy SL. Neuroleptic malignant syndrome and malignant hyperthermia: end of a controversy? J Neuropsychiatry Clin Neurosci 1995;7(02):135–144
13 Ullah W, Cheema MA, Ashfaq A, et al. A rare association of Takotsubo cardiomyopathy with neuroleptic malignant syndrome. J Community Hosp Intern Med Perspect 2020;10(02): 133–137
14 Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry 2004;65(04):464–470
15 Oomura M, Terai T, Sueyoshi K, Shigeno K. Reversible cardiomyopathy as the autonomic involvement of neuroleptic malignant syndrome. Intern Med 2004;43(12):1162–1165
16 Velamoor VR. Neuroleptic malignant syndrome. Recognition, prevention and management. Drug Saf 1998;19(01):73–82
17 Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: a review. Psychiatr Serv 1998;49(09):1163–1172
18 Caroff SN, Mann SC, Sullivan KA, Campbell EC. Neuroleptic malignant syndrome. In: Movement Disorder Emergencies. Springer; 2022:95–113
19 Erermis S, Bildik T, Tamar M, Gockay A, Karasoy H, Ercan ES. Zuclopenthixol-induced neuroleptic malignant syndrome in an adolescent girl. Clin Toxicol (Phila) 2007;45(03):277–280