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Gloria Akuamoah-Boateng, Kayla A Buttafuoco, Courtney C Sutton, Brian P Hackett.

Affiliations below.

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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 anti-dopaminergic 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 neuroleptic malignant syndrome 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.

Corresponding Author:
MBChB Gloria Akuamoah-Boateng, Monroe Carell Junior Children's Hospital at Vanderbilt, Pediatrics, 2200 Children's Way, 37232-0005 Nashville, United States, gloria.akuamoah-boateng@vumc.org

Affiliations:
Gloria Akuamoah-Boateng, Monroe Carell Junior Children's Hospital at Vanderbilt, Pediatrics, Nashville, United States
Kayla A Buttafuoco, Vanderbilt University School of Medicine, Nashville, United States
Courtney C Sutton, Monroe Carell Jr Children's Hospital at Vanderbilt Department of Pharmacy, Nashville, United States
Brian P Hackett, Monroe Carell Junior Children's Hospital at Vanderbilt, Pediatrics, Nashville, United States

NEUROLEPTIC MALIGNANT SYNDROME IN A 10-MONTH-OLD EX-PRETERM INFANT WITH DELIRIUM

Gloria Akuamoah-Boateng, MBChB[1], Kayla A Buttafuoco[2], Sutton, Courtney C, PharmD[3]

Hackett, Brian Paul, MD[4]

[1]Department of Pediatrics-Division of Neonatology, Monroe Carell Jr. Children's Hospital at Vanderbilt, **Email:** gloria.akuamoah-boateng@vumc.org

[2]Vanderbilt University School of Medicine**, Email**: kayla.a.buttafuoco@Vanderbilt.Edu

[3]Department of Pharmacy-Monroe Carell Jr. Children's Hospital at Vanderbilt, **Email**: Courtney.c.sutton@vumc.org

[4]Department of Pediatrics-Division of Neonatology, Monroe Carell Jr. Children's Hospital at Vanderbilt, **Email**: brian.hackett@vumc.org

CORRESPONDING AUTHOR: Gloria Akuamoah-Boateng

Monroe Carell Jr. Children's Hospital at Vanderbilt

2200 Children's Way

Nashville, TN 37232

Gloria.akuamoah-boateng@vumc.org

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 anti-dopaminergic 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 neuroleptic malignant syndrome 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 weeks, 6 days preterm infant with esophageal atresia, broncho-gastric fistula, and right lower lobe pulmonary sequestration with a large aortopulmonary collateral underwent multiple surgeries requiring a prolonged course of post-operative 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 temperature of 42.9°C. Examination was significant for intermittent, non-suppressible 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 (CRP), lactic acidosis, transaminitis, and acute kidney injury (AKI). Electrocardiogram (EKG) 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 (CK) 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 (DIC), transaminitis, and worsening AKI.

Due to concern for neuroleptic malignant syndrome, olanzapine was stopped on the day of acute decompensation, and bromocriptine was initiated at 0.625 mg/day, which was later increased to 1.25 mg/day. 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 forty-eight hours. Given his grim prognosis, care was re-directed, 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^{o} 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 > 1000 IU/L, 5) leukocytosis, and 6) tachycardia, a diagnosis of neuroleptic malignant

syndrome (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:

Neuroleptic malignant syndrome (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 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 creatinine phosphokinase, leukocytosis, acidosis, and AKI. A creatinine phosphokinase level greater than 1000 IU/L is specific to NMS, with the degree of elevation correlating with disease severity and prognosis [16,17]. Our patient had markedly elevated creatinine phosphokinase levels peaking at >5000 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 non-specific 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 (DVT) 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 5-25% and is usually due to effects of dysautonomia and multi-organ dysfunction[17,19.] Of note, described outcomes are generally for older patients and outcome data for infants is 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 pre-existing 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. *The Neurohospitalist*. 2011;1(1):41-47.

2. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology*. 1981;31(2):132-132.

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(2):135.

4. van Rensburg R, Decloedt EH. An approach to the pharmacotherapy of neuroleptic malignant syndrome. *Psychopharmacol Bull*. 2019;49(1):84.

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(7):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(4):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(5). https://journals.lww.com/psychopharmacology/fulltext/2023/09000/neuroleptic_malignant_syndrome_in_a_15_month_old.12.aspx

8. Carbone JR. The neuroleptic malignant and serotonin syndromes. *Emerg Med Clin*. 2000;18(2):317-325.

9. Kunz M, Gomes FA, Tramontina JF, Kapczinski F. Late-Onset Neuroleptic Malignant Syndrome in a Patient Using Olanzapine. *J Clin Psychopharmacol*. 2007;27(3). https://journals.lww.com/psychopharmacology/fulltext/2007/06000/late_onset_neuroleptic_malignant_syndrome_in_a.13.aspx

10. Strawn JR, Keck PE, Caroff SN. Neuroleptic Malignant Syndrome. *Am J Psychiatry*. 2007;164(6):870-876. doi:10.1176/ajp.2007.164.6.870

11. Kubo S ichi, 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, Caroff SN, McElroy SL. Neuroleptic malignant syndrome and malignant hyperthermia: end of a controversy? *J Neuropsychiatry Clin Neurosci*. Published online 1995.

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(2):133-137. doi:10.1080/20009666.2020.1742522

14. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry*. 2004;65(4):464-470. doi:10.4088/jcp.v65n0403

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. *Drug Saf*. 1998;19(1):73-82.

17. Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: a review. *Psychiatr Serv*. 1998;49(9):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*. 2007;45(3):277-280.