

# Neuroleptic Malignant Syndrome: Early Diagnosis Saves Lives in Low-Resource Settings

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**Context:** Neuroleptic malignant syndrome (NMS) is an uncommon but serious adverse event to antipsychotic medications.

**Case Details:** A 14-year-old Ugandan lady presented with high grade fevers, multiple convulsions, altered mentation and lead-pipe rigidity following an intramuscular injection of zuclopenthixol acetate (as Clopixol-Acuphase®). Her labs were significant for elevated aminotransferases and leucocytosis. She had a normal brain CT scan, renal function and cerebrospinal fluid analysis. Discontinuation of Clopixol, administration of bromocriptine 5mg once daily and dantrolene 25mg three times a day and supportive treatment resulted in a complete neurological recovery within 4 weeks of the onset of symptoms.

**Discussion:** Early diagnosis and prompt supportive therapy are required to reduce mortality and morbidity. Early recognition of symptoms and discontinuation of offending agent by health care providers are needed to have recovery even in settings with limited resources.

**Keywords:** neuroleptic malignant syndrome, zuclopenthixol acetate, Uganda

## Introduction

Neuroleptic malignant syndrome (NMS), characterized by four major clinical symptoms of hyperthermia, extreme muscle rigidity, autonomic instability, and mental status changes, is an uncommon life-threatening neurological emergency due to an idiosyncratic reaction to antipsychotic drugs; usually associated with high-potency first-generation neuroleptic agents but also may be caused by low-potency and atypical antipsychotic agents.<sup>1-3</sup> Use of dopamine-receptor antagonist medications such as antiemetics, tricyclic antidepressants, and lithium or rapid withdrawal of dopaminergic medications, such as those used in the treatment of Parkinson's disease are also associated with NMS.<sup>2</sup>

NMS has been reported in about 0.01% to 3.3% of patients taking typical neuroleptic medications, mainly in young adults and is reported to be as twice as common in men than it is in women.<sup>1,2</sup> However, the incidence is much lower with atypical anti-psychotics, and frequently occurs in middle-aged men than women in the ratio of 5:1.<sup>3</sup> Therefore, the second-generation antipsychotics are preferred as the first-choice treatment especially in first-episode psychosis and young people.<sup>4</sup>

Untreated NMS is almost always fatal. With increasing awareness, early diagnosis and intensive care management, mortality attributable to a treated NMS has significantly reduced from over 30% to less than 10% in recent reports.<sup>2</sup>

Herein, we report a case of NMS following administration of zuclopenthixol acetate in a Ugandan girl with a first-episode manic disorder.

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## Case Presentation

A 14-year-old lady was referred to our Neurology services from a tertiary mental health hospital with concerns of persistently very high-grade fevers, altered mental status and convulsions for a week.

Prior to admission in the mental health hospital, she presented with a 2-week history of aggressive behaviour, wandering away from home and over talkativeness. She was otherwise previously well with no known personal or family history of mental illness. A diagnosis of a first-episode acute mania was made and she was started on intramuscular zuclopenthixol acetate (as Clopixol-Acuphase<sup>®</sup>) 25mg stat.

Forty-eight hours after administration of zuclopenthixol, she developed high-grade fevers with temperatures between 38°C to 42°C over several days. This was associated with multiple generalised tonic-clonic convulsions each lasting about 5 minutes. These were associated with alteration in mental state, frothing from the mouth, post-ictal sleepiness, and loss of bowel and bladder control. She had no post-ictal paralysis. These seizures lasted for over a week. There were no features suggestive of primary catatonia, such as extreme negativism and an unusual movement. However, she reported no history of headache, vomiting, blurring of vision or yellowing of eyes. She did not have a flu-like syndrome, joint swellings, bleeding under the skin or skin rash. Review of other systems was essentially normal. She was not on any chronic medication and had no history of physical trauma. She was initiated on Paracetamol 1g three times a day with no response in temperature reduction. A work up for infective causes was non-yielding. A provisional diagnosis of malignant hyperthermia was made and prompted an urgent referral for specialised neurology care.

On admission to the Neurology unit, examination revealed a sick looking young lady, drooling saliva and tremulous. Her Glasgow coma scale (GCS) was 8/15 (E4, V1, M3), temperature 39.4°C, blood pressure 107/66 mmHg, pulse rate 107 beats per minutes, random blood sugar 9.6 mmol/L, respiratory rate 22 breaths per minute. Her oxygen saturation was at 97% on ambient air. She had generalised lead-pipe rigidity with appreciable nuchal rigidity but negative Kerning's sign. She had a reduced muscle power in all limbs (3/5), normal deep tendon reflexes and a negative Babinski's reflex. Her pupils were equal, accommodative and reactive to light. The remainder of the physical examination was unremarkable.

Her complete blood count revealed a haemoglobin concentration 9.5g/dl, a raised total white cell count of

21.26x10<sup>9</sup> cells/L predominantly neutrophils (20.66x10<sup>9</sup>cells/L), and a platelet count 122x10<sup>9</sup>/L. Her urea, creatinine and electrolytes were within normal limits. Her alanine aminotransferase and aspartate aminotransferase were 219 units (x5.5 upper limit of normal (ULN)) and 106 units (x2.65 ULN), respectively. There was no myoglobinuria on urinalysis other urine parameters were within normal limits. Total bilirubin level was 5.4 (reference range: <3.4) micromoles per litre. A lumbar puncture was done to exclude an on-going CNS infection and had a normal opening CSF pressure, revealing normal CSF chemistry and no organisms were demonstrated on a gram staining and India ink preparations. Chest x-ray and computed tomography of the brain were normal. We were unable to obtain serum creatinine phosphokinase levels to rule out rhabdomyolysis.

Based on the above findings, a diagnosis of neuroleptic malignant syndrome was made. We stopped Clopixol-Acuphase. Phenytoin 200mg twice daily, dantrolene 25mg three times a day and bromocriptine 5mg once a day were commenced via nasogastric tube. Supportively, nasogastric tube and urinary catheter were inserted, cold intravenous crystalloid fluid administered; cold tepid sponging and axillary ice packs were commenced. We monitored GCS, vitals and urine output four hourly. She received daily physical therapy during hospitalisation through our physiotherapy services.

She was afebrile within a week and her GCS improved to 15/15 over a period of 3 weeks without being admitted in the intensive care or high dependency units. In addition to the complete neurological and physical recovery at the neurology unit, she also remained calmed and free of psychiatric symptoms and she was eventually discharged through the mental health unit.

## Discussion

There are a growing number of patients with schizophrenia, schizoaffective disorders and bipolar affective disorders in our community who requires long-term anti-psychotic therapy for the control of their symptoms. Thus physicians should be aware of adverse events to these agents, including NMS since they can occur at anytime during the treatment of these mental disorders. The present case illustrates the occurrence of NMS in an anti-psychotic naïve Ugandan young girl following intramuscular administration of zuclopenthixol acetate.<sup>5</sup> The onset of NMS in our patient was so dramatic, occurring after 48 hours after administration of the anti-psychotic agent. In literature, on average, onset was

between 4 and 14 days after the start of therapy, with 90% of cases occurring within 10 days.<sup>6</sup> It is also important to note that NMS can occur years into therapy.

NMS, previously described as “syndrome akinétique hypertonique” (hypertonic akinetic syndrome), is an uncommon, but potentially life threatening complication of neuroleptic drugs.<sup>3</sup> Several agents that interact with the dopaminergic, serotonergic and noradrenergic pathways have been shown to be associated with NMS.<sup>3,7</sup> All age groups are susceptible to NMS, although the disease disproportionately affects men. The underlying pathophysiology remains poorly understood, however, its thought that NMS occurs because of dopamine receptor blockade inside the neurons of the nigrostriatal tract, mesocortical pathway and hypothalamic nuclei by neuroleptics and excessive calcium release from the sarcoplasmic reticulum of skeletal myocytes.<sup>8</sup> Also, the role of the serotonergic and noradrenergic receptor blockers has been suggested, especially in patients treated with low-potency dopaminergic receptor blockers such as atypical antipsychotics.<sup>3</sup> Above all these are genetic factors, which plays an important role in the pathogenesis of NMS.

The classic cardinal symptoms of NMS i.e. hyperthermia, extrapyramidal symptoms, altered mental status and autonomic dysfunctions are not pathognomonic of this syndromes.<sup>9</sup> As such, NMS remains a diagnosis of exclusion leading to misdiagnoses and delayed initiation of treatment. However, a rapidly progressive development of the cardinal NMS symptoms following administration of an NMS-inducing agent is highly suggestive of this syndrome and should a raise an index of suspicion to the clinical team. The occurrence of recurrent tonic-clonic convulsions in our patients was unusual. However, with a normal chest and brain imaging and a normal CSF analysis, the index of suspicion for NMS was high.

No single laboratory (lab) test has been shown to confirm the diagnosis of NMS. However, lab tests are key aiding the diagnosis of NMS, ruling out differential diagnoses and look for complications of the disease. Key lab findings in NMS include increased levels of serum creatinine phosphokinase, leucocytosis and mild elevation in hepatic enzymes.<sup>1</sup> As seen in our case, extensive investigation to rule out complications and differential diagnoses are key in NMS and yet remains a big challenge in low resource settings. We were unable to do serum creatinine phosphokinase, a key marker of rhabdomyolysis – a deadly and yet a very common complication of NMS.

Management of NMS entails discontinuation of the implicated antipsychotic, administration of dopamine receptor agonists, supportive care and other adjunctive pharmacological interventions results to complete resolution of symptoms without consequential neurological deficits in a vast majority of patients. There is no established treatment of NMS based on randomised clinical trials. Expert opinion and case reports recommends the use of a combination of dantrolene and bromocriptine for the pharmacological management of NMS.<sup>10</sup> A recent report categorised pharmacological management of NMS based on severity of symptoms. In mild disease, monotherapy of benzodiazepines was suggested. Amantadine or bromocriptine plus benzodiazepines for moderate disease and dantrolene plus amantadine or bromocriptine plus benzodiazepines for those with severe NMS.<sup>11</sup> All patients with NMS require aggressive supportive management, including hydration, correction of electrolyte imbalances and cardiorespiratory support in the intensive care unit.

A recent analysis of international treatment guidelines for NMS found that only 9 guidelines reported concrete therapy recommendations in the settings of schizophrenia, most of which had very low level of evidence.<sup>4</sup> The authors concluded that the lack of knowledge about the NMS and its treatment might delay the onset of therapy, impair the quality of treatment, and lead to a worse outcome or death. This is particularly true in low-resource settings where such guidance may not be available and awareness for this life-threatening condition is very low.

Electroconvulsive therapy has been used in some patients with progressive disease despite the aforementioned management approach.<sup>9</sup> Delayed diagnosis of NMS results in progressive neurological deterioration, prolonged hospital stay, complications such as rhabdomyolysis and death<sup>8-10</sup>.

Given the increasing off label prescription of both first and second generation of antipsychotics in certain forms of dementias, severe insomnia, and autistic spectrum disorders in children, other specialists and general practitioners should be aware of NMS. Increased awareness among clinicians, earlier diagnosis, and intensive care intervention are some of the key factors that have led to the recent significant reduction in the morbidity and mortality associated with NMS globally.<sup>8</sup>

In conclusion, though rare, neuroleptic malignant syndrome may occur in young adult females following the administration of atypical antipsychotics, anaesthesia and

surgery. Early diagnosis and prompt supportive measures are essential to reduce morbidity and mortality.

## Ethics

The patient's parent has provided written informed consent to have the case details published. Institutional approval was not required to publish the case details.

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## Disclosure

All authors declare they don't have conflict of interests.

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