Widening spectrum of neuroleptic malignant syndrome: Case series

Gunchan Paul, Sachi Singhal[1], Birinder S. Paul[2], Gurparvesh Singh[3], Shriya Goyal[3]

Departments of Critical Care Medicine and [2]Neurology, Dayanand Medical College and Hospital, [3]MBBS Dayanand Medical College and Hospital, Ludhiana, Punjab, India, [1]MMBS MD, Crozer Chester Medical Center, Upland PA, US

Abstract

Neuroleptic malignant syndrome (NMS) is a rare and rapidly progressive syndrome with mortality rate of 5.6%. The spectrum of onset, progression and outcome is heterogeneous and is associated with number of risk factors. In our case series, we entail the triggers, hospital course and outcome of five interesting in-patient cases that were admitted to our service in a tertiary care hospital in Northern India. This case series is to highlight the first ever reported case of NMS triggered by levosulpiride administration, along with one of the few first cases of NMS after programming of DBS, hypothyroid disorders, levodopa readjustment and selective basal ganglia and cerebellar injury following the hyperthermic syndrome. This is also to bring to attention of clinicians worldwide the atypical risk factors of NMS, and stress the importance of staying vigilant for the same by frequent follow-ups and high degree of clinical suspicion. We also aim to generate epidemiological data about these atypical triggers.

Keywords: NMS is a rare condition with mortality rate and requires early identification of the syndrome with high clinical suspicion. We hereby report five different triggers for hypo-dopaminergic state leading to NMS to sensitize the physicians regarding the atypical risk factors

Introduction

Neuroleptic malignant syndrome (NMS) is a rare syndrome with prevalence ranging from 0.02 to 3.2% in patients on neuroleptic medications.[1] It is rapidly progressive and lethal condition with mortality rate of 5.6%.[2,3] However, its incidence is now decreasing due to the use of newer agents and increased awareness of the condition among clinicians. The spectrum of onset, progression and outcome is heterogeneous and is associated with a number of risk factors. The risk factors can be grouped into four categories as demographic factors (age, co-morbidity); genetic factors (history of previous NMS, family history of catatonia, channelopathy); environmental (high ambient temperature, dehydration); and most importantly the pharmacological risk factors (type of drug, pharmacokinetics, polypharmacy). NMS is usually associated with the administration of dopamine antagonists or high-potency first-generation neuroleptic agents.[4]

The diagnosis of NMS in patients with Parkinson's disease (PD) is a clinical challenge. As the name suggests, the term neuroleptic may inhibit the consideration of the diagnosis of NMS when the offending pharmacological manipulation does not involve neuroleptic drugs. Also, there is less appreciated proposed mechanism of NMS in PD patients which involves the disruption of the striatal dopaminergic drive

Address for correspondence: Dr. Birinder S. Paul,
Professor, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana.
E-mail: drbirinder06@yahoo.co.in

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because of withdrawal, reduction or alteration of dopaminergic therapy causing *acute dopamine depletion syndrome* leading to NMS-like syndrome.[5]

Though, case series are the lowest level of evidence, in rare clinical conditions they play an important role to fill in the literature gap and guide future research. We present a series of five patients of Parkinsonism with NMS of whom four had pharmacological- and one had medical-related hypo-dopaminergic crisis as a risk factor for NMS.

Case 1

NMS following Deep Brain Stimulation (DBS)

A 70-year-old male with Parkinson's disease for 11 years was being managed with levodopa (600 mg/day), pramipexole (6 mg/day) and amantadine 300 mg/day (LED: 1500 mg). Due to the gradual increase in levodopa fluctuations and peak-dose dyskinesias, he underwent bilateral Sub-thalmic nucleus (STN)-DBS in July, 2019. Programming of DBS was done 4-6 weeks post-surgery. The dose of levodopa was reduced from 600 mg/day to 300 mg/day and pramipexol was stopped (LED reduction 60%). Seven days later, he presented to the emergency department with complaints of high-grade fever (106°F) and altered mental status. For the next few hours temperature continued to rise accompanied with worsening of sensorium. He was shifted to the Intensive Care Unit (ICU) for further management. On admission to the ICU, heart rate was 126 beats/min, respiratory rate 32 breaths/min and blood pressure (BP) of 90/60 mmHg. Systemic examination revealed no meningeal signs, normal pupillary size and reaction but generalized muscle rigidity. During the ICU stay, wide variations in heart rate and BP were noted along with profuse sweating.

Laboratory investigations revealed total leucocyte count (TLC)-18,000/mm^3, serum creatinine 1.7 mg/dL and elevated creatinine phosphor-kinase (CPK) 2,847 units/L.Non contrast computerized tomography of the brain showed correct placement of the electrodes and no evidence of bleed. Evaluation for infectious etiology including chest X-ray, procalcitonin (PCT), urine and blood culture and cerebro-spinal fluid (CSF) analysis were negative. During hospital course, patient continued to have non-resolving high-grade fever (107°F), altered mental status, autonomic instability and elevated CPK. With the differential diagnosis of neuroleptic malignant hyperthermia, he was started with dantrolene along with lorazepam. The dose of levodopa was increased to 600 mg/day along with aggressive supportive medical care to control temperature. Within the next 24 h, his temperature came down to 98.9°F and hemodynamics were stable. CPK levels started decreasing and the patient was ambulatory after 7 days. Though, he improved initially, he developed nosocomial sepsis and died after 3 weeks due to multiorgan failure.

Case 2

NMS after alteration of dopaminergic therapy

A 61-year-old male had PD for 7 years and was being managed with levodopa 900 mg/day, ropinirole 3 mg/day and amantadine 200 mg but was experiencing fluctuations in disease status including peak-dose dyskinesia, unpredictable OFF and gait freezing. In view of the marked disability, levodopa was reduced to 500 mg/day. Two days after the dose reduction, he was admitted to neurology emergency with high-grade fever (104°F), tachycardia and altered sensorium.

On examination, the heart rate was 136 beats/min, respiratory rate 30/min and oxygen saturation of 94% on room air. He was drowsy with generalized muscle rigidity and normal pupils and no meningeal signs. Systemic examination was normal. Evaluation for infective etiologies revealed TLC of 13,500/mm^3, creatinine 1.4 mg/dL, PCT 0.10 ng/mL and CPK 1,556U/L. Blood culture, urine culture and ultrasound of abdomen were normal. The patient continued to have high-grade fever, severe muscular rigidity, altered sensorium and elevated CPK. In view of history of PD and withdrawal of dopaminergic medications prior to onset of symptoms, NMS was considered.

He was managed with dantrolene and levodopa was also stepped up to 900mg/day along with aggressive control of temperature. Gradually, there was clinical improvement with resolution of fever and rigidity; normalization of TLC count and CPK. Mental status improved to full recovery by the third day and he was discharged in stable condition after 1 week on 900mg of levodopa/day.

Case 3

NMS in levosulpiride-induced Parkinsonism

A 45-year-old male sustained multiple contusions tothe brain after a road accident for which he was managed conservatively at a local hospital. Two months later, he presented to the emergency department with tremors in the left hand, rigidity and bradykinesia [Video 1a]. On examination, he had generalized rigidity with marked bradykinesia. Hence, he was diagnosed with Parkinsonism. NCCT-brain was done to look for post-traumatic hydrocephalous or sub-dural haematoma but was normal. Detailed review of his treatment records revealed that he was on levosulpiride (75 mg/day) for the last 2 months as advised on his discharge summary. As he

had features of Parkinsonism with tremors, the offending drug was stopped and levodopa (150 mg/day) was started, which resulted in improvement in rigidity and bradykinesia. Two days later, he developed fever and restlessness; fever continued to rise despite antibiotics and mental status also deteriorated; generalized rigidity reappeared over the next 3 days.

Examination revealed restlessness with localization to painful stimulus, no meningeal signs and normal pupils. Generalized muscle rigidity was evident. Work-up for infective etiology was negative with elevated CPK (19,000 U/L) confirming the diagnosis of NMS. He was managed for NMS and CPK levels returned to baseline within 5 days. He was discharged after 10 days and on follow up after 1 month, he was normal with no tremors, bradykinesia or rigidity [Video 1b]. To the best of our knowledge, this is the first case report of NMS after sudden discontinuation of levosulpiride.

Case 4

NMS with hypothyroid disorder

A 72-year-old gentleman was admitted with restlessness and fever for 1 day. Within 24 hours, he developed tachypnea, tachycardia and muscular rigidity with deterioration in sensorium. He had high-grade fever of 105°F, not responding to anti-pyrectics and intravenous antibiotics for 4 days. Past treatment history revealed that he was on regular treatment with antipsychotic olanzapine 10 mg/day and estalopam 20 mg/day for his behavioral changes since the last 3 months. This history was not disclosed at the time of admission. On examination, the patient was arousable to verbal commands. Vitals revealed fever of 102°F, heart rate 102 beats/min, respiratory rate 24/min. There were nomeningeal or focal neurological signs with associated generalized muscle rigidity.

Hematological investigation revealed leukocytosis with TLC 16,450/mm^3, liver and renal function tests showed only mild abnormalities while infective screening including blood, urine culture, PCT and CSF studies were negative and computerized tomography brain was also normal. Serum CPK was 3,709 IU/L. In view of the prior use of antipsychotic drugs, clinical finding and elevated CPK levels, the patient was treated for NMS with hydration, injectable benzodiazepine along with external cooling. There was no significant improvement in his sensorium. Later, his blood investigation revealed high Thyroid stimulating hormone (TSH) levels (50 IU/L) with normal anti-thyroid peroxidase (TPO) antibody, and hence, started on thyroxin 0.1mg/day along with other supportive treatment. He improved considerably over the next few days and serum CPK also settled to normal. He was discharged on oral thyroxine 0.1/day after 1 week in stable condition.

Case 5

NMS inflicting brain injury

A 60-year-old male with Parkinson's disease for 10 years was on medical treatment on daily dose of levodopa 800 mg/day, ropinirole 6 mg/day, amantadine 200 mg/day, rasagiline 1 mg/day (LED-1170). The patient had cough with respiratory symptoms. He isolated himself and stopped his medications for PD assuming it to be COVID-19 infection. Two days later, he presented to emergency with a fever of 105°F, difficulty in breathing and rigidity. On arriving in the emergency, he required mechanical ventilation for respiratory failure. He was managed with antibiotics for his chest infection. He was shifted to the ICU as he tested negative for COVID-19. He had fever of 105°F, heart rate104/min, with generalized rigidity and altered sensorium without any focal neurological signs.

Laboratory investigations revealed TLC 19,000/mm^3, serum creatinine 1.9 mg/dL, CPK 10,345 units/L. PCT, urine and blood culture and CSF analysis were all negative for any infectious cause. He continued to have non-resolving high-grade fever (103°F), persistent altered sensorium, autonomic instability and elevated CPK. With the differential diagnosis of neuroleptic malignant hyperthermia, he was started on lorazepam 4 mg/day, levodopa 500 mg/day and amantadine 200 mg/day. Gradually, his fever and CPK levels returned to baseline and his sensorium improved. In spite of improvement in his general condition, he remained in mute state. MRI done at this stage showed bilateral T2 hyperintensities in the deep cerebellar white matter with corresponding restricted diffusion and small focus of restricted diffusion in the left basal ganglia [Figure 1]. He was discharged with tracheostomy *in situ* and LED of 720 mg.

Discussion

The aim of this case series is to highlight the possible risk factors for the development of NMS in PD patients. Most of the NMS cases in literature are associated with administration of dopamine receptor antagonist or sudden alteration in their dosage.[6] A lesser discussed yet equally significant entity and unusual cause of NMS other than dopamine antagonism is the disrupted striatal dopaminergic drive because of dopamine agonist. To the best of our knowledge, this is the first presentation of a case series of five patients with pharmacological- or medical-related hypo-dopaminergic crisis leading to features of NMS along with the first case report of NMS in PD after sudden discontinuation of levosulpiride (Case3). Although, NMS with olanzapine is well documented, no prior case of NMS with hypothyroidism (Case4) on olanzapine exists in literature. There is no previous report in literature with

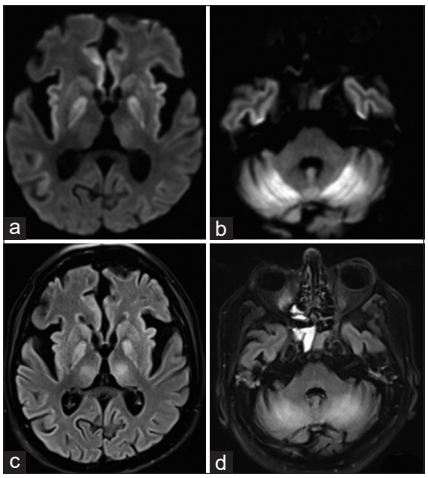

Figure 1: MRI (diffusion-weighted) shows symmetric area of restriction diffusion in globus pallidus, subthalamic nuclei, insular cortexand medial frontal cortex in (a) and corresponding FLAIR in (c). MRI (diffusion-weighted) shows symmetric area of restriction diffusionin cerebellar hemispheres in (b) and corresponding FLAIR in (d)

selective involvement of cerebellum and basal ganglia (Case5) following NMS in PD patient.

Similarities and differences between the profile of reported NMS cases and our series

The profile of our patients with atypical risk factors is similar to those of reported NMS in certain aspects. All our patients were males and this is in concordance with existing literature that suggests NMS is common in males.[7] However, characteristic such as age, offending agent and co-morbidity profile were found to vary between the described cases in literature and our observation [Table 1]. According to a recent systematic review, NMS peaks at theage of 20-25 years, butin contrast, only one of our patients was of 45 years and the remaining were of more than 60 years.[8] Only one was on regular atypical antipsychotic medication without any dosage alteration [Table 1].

What makes this atypical cause: Pathophysiology and drugs

Disruption of dopamine-mediated signaling was the probable reason for NMS in our patients. The degeneration of dopamine neurons leads to loss of dopaminergic transmission in PD. The abrupt withdrawal or change of dosage of levodopa, dopamine agonist with very short half-life, may precipitate NMS in these patients.[4]The proposed mechanism could be sudden decrease in postsynaptic receptor stimulation or blockade of the postsynaptic receptor or lack of neurotransmitter. All patients had different triggering factors but the denominator was the lack of dopaminergic signaling which was of paramount importance in leading to the clinical features of NMS in these cases.

As the application of DBS in the treatment of Parkinson's disease continues to expand, awareness of this potential complication becomes increasingly important. NMS in post-DBS patients as in Case I has been reported in three cases, two of which had battery failure rather than levodopa dose reduction.[9,10] Though NMS following abrupt withdrawal of levodopa is abundant, yet to the best of our knowledge there is no documentation of NMS post-reduction of dose for peak-dose dyskinesia as in Case II.

In Case III, whether the withdrawal of levosulpiride (dopamine antagonist) or start of levodopa (dopaminergic agent) was the precipitant cause of NMS remains unanswered. Paroxysmal hyperpyrexia syndrome (PHS) is a differential in such clinical presentation as it is a group of acute dysautonomia which shares common features with NMS.[11] While NMS is triggered by the use of neuroleptic agents, PHS occurs most commonly in the setting of rapid-dose titration or withdrawal of dopamine agonists. These disorders can, however, be differentiated by the detailed drug history and setting in which they occur.

Increased dopaminergic activity has been noticed in hypothyroid animal models along with elevated TSH levels that cause increase in the number of thyrotrophic dopamine receptors.[12] Also thyrotropin-releasing hormone induces increase in the sensitivity of postsynaptic dopamine receptors in the striatum and limbic forebrain. Hence, in Case IV, NMS might have developed when the excess dopaminergic activity was inhibited by the neuroleptic agent with an underlying untreated hypothyroidism.[13] MRI findings of Case V revealed bilateral T2 hyperintensity in the deep cerebellar white matter with corresponding restricted diffusion and small focus of restricted diffusion in the left basal ganglia [Figure 1]. This is an unusual presentation as it represents hyperpyrexia-induced changes in cerebellar and basal ganglia that are particularly susceptible to thermal damage.[14]

Challenges in diagnosing atypical cases

The issue of underdiagnosis of NMS is of significant concern as this condition is a neurological emergency and delay in diagnosis may increase morbidity and mortality. Characteristically, NMS involves a tetrad of distinctive clinical features including fever, rigidity, changes in mental status and autonomic instability.[15] Clinical suspicion should be high on cards if two or more features along with risk factors are present. The most important step in diagnosing NMS is to obtain a good clinical history including detailed and comprehensive drug history of all medications, duration, dose and sequence of administration. In addition, extensive work-up is also needed to rule out central nervous system (CNS) infection. Also, elevated CPK >1,000 IU/L serves as an important diagnostic marker for NMS and measuring serial levels also helps in monitoring the fatal condition.

These cases were worth reporting as each of our patients presented with a different trigger for hypo-dopaminergic state

Table 1: Clinical characteristics of patients with neuroleptic malignant syndrome

Age/ Sex	Duration of PD; Hoehn and YahrStage	Treatment History	Comorbidity	Clinical Presentation	CPK Levels	Risk factor for NMS	Management	Outcome
70/M	11 years; 3	Levodopa: 600/day Pramipexol: 6 mg/day Amantadine: 300 mg/day LED: 1500 mg	-	Fever-101°F * Rigidity Autonomic dysfunction*	2847	Dose reduction of levodopa 4-6 weeks post-STN-DBS	Supportive medical care and cooling, Dantrolene, Lorazepam Levodopa dose increased	Death
61/M	7 years; 4	Levodopa: 900/day Ropirinolol: 3 mg/day Amantadine: 200 mg/day LED: 1500 mg	Hyper tension	Shortness of breath Fever 101°F Tachycardia Altered sensorium	1556	Dose reduction of levodopa post peak dose dyskinesias	Dantrolene Lorazepam Levodopa dose increased	Discharged
45/M	6 months; 2	Levosulpiride (since 2 months) Levodopa: 150 mg/day LED-	-	Fever 106°F Altered sensorium, Restlessness Rigidity	19000	Levosulpiride withdrawal and start of levodopa	Lorazepam Supportive treatment	Discharged, video outlines first follow up visit
72/M	4 years; 2	Olanzapine: 10 mg/day Estalopam: 20 mg/day	Hypothyroid	Vomiting Altered sensorium Fever 103°F Rigidity	3709	Atypical anti -psychotic olanzapine & untreated thyroid disease	Lorazepam Thyroxine Supportive treatment	Discharged
60/M	10 years; 4	Levodopa: 800 mg/day Ropinirole: 6 mg/day Amantadine: 200 mg/day Rasagiline: 1 mg/day LED: 1170	Hyper tension	Shortness of breath Fever 105°F Tachycardia Altered sensorium	10347	Stopped levodopa due to suspected COVID-19 infection	Lorazepam Levodopa Supportive treatment	Discharged with tracheostomy in situ

leading to NMS. Such cases not only sensitize the physicians regarding the atypical risk factors of NMS but also generate epidemiological data about the same.

Implications of recognizing atypical cases- Learning Pearls:

- NMS is a rare yet potential disaster waiting to happen
- Early identification of the syndrome is possible with high index of clinical suspicion
- Identification of the offending agent and its discontinuation is of utmost importance
- Screening for co-morbidities is helpful, as that might be the potential trigger
- Early recognition and implementation of treatment for NMS cannot be stressed enough

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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