Neuroleptic Malignant Syndrome (NMS) Management

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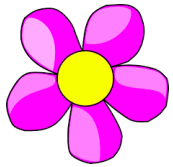
Neuroleptic Malignant Syndrome (NMS)

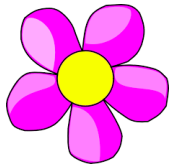
Types



- Afebrile NMS
  - Less malignant, short lasting, good prognosis
- Classical NMS
  - Malignant, long lasting, guarded prognosis

Neuroleptic Malignant Syndrome (NMS)

Types



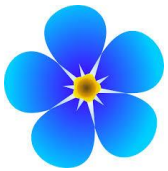
- On neuroleptics
- On withdrawal of neuroleptics or dopaminergic agonists

Afebrile Neuroleptic Malignant Syndrome associated with Fluphenazine decanoate:

A case report

(Assareh M1, Habibi LK. Iran J Psychiatry. 2010 Spring;5(2):78-80.)

- We present this case to alert the clinicians to the potential for inducing afebrile NMS. A 41, man with a history of schizophrenia, presented with decreased level of consciousness, muscular rigidity, waxy flexibility, mutism, generalized tremor, sever diaphoresis and tachycardia which progressed during the 24 h, two weeks after receiving 12.5 mg of fluphenazine decanoate and following the 3rd session of ECT



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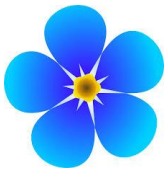
Afebrile Neuroleptic Malignant Syndrome associated with Fluphenazine decanoate:

A case report

(Assareh M1, Habibi LK. Iran J Psychiatry. 2010 Spring;5(2):78-80.)

- Investigations indicated primarily leukocytosis, an increasing level of CPK (Day-1 = 92 IU/L, Day-2 = 2800 IU/L, Day-3 = 4880 IU/L) and hypokalemia during the next 72 hours
- In order to overcome muscle rigidity and antipsychotic-induced dopamine receptor blockade the patient was given supportive medication: dantrolene and bromocriptine



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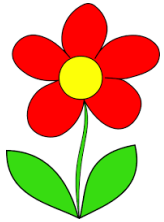
Neuroleptic malignant syndrome without fever: a report of three cases (Case-1)

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

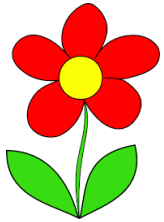
- A 52, man, on treatment for post-psychotic depression presented after an act of deliberate self poisoning with a rodenticide. As he became acutely disturbed and violent he was given several injections of intramuscular haloperidol, and he received no further antipsychotic medication
- On the next day he developed severe rigidity associated with profuse sweating and marked autonomic instability. His heart rate was 120 bpm and was irregular. His BP showed wide fluctuations and there was urinary incontinence. He then became confused and went into a state of semi-consciousness. There was no increase in body temperature



Neuroleptic malignant syndrome without fever: a report of three cases (Case-1)

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- The CPK was 1575 IU, 6771 IU on 2nd & 4th day, the WBC count was 17 000/mm^3.
- As the patient did not have any increase in body temperature there was doubt as to the diagnosis. However, a Medline search contained reports of three patients with NMS in the absence of fever
- The patient was immediately started on bromocriptine at a dose of 2.5 mg TDS
- By the 5th day his condition improved with the autonomic disturbances disappearing and the rigidity subsiding. His CPK became normal after 5 days of treatment



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Neuroleptic malignant syndrome without fever: a report of three cases (Case-2)

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- A 20, man, on 10 mg trifluperazine BD, for schizophrenia with catatonic features was discharged after being given a depot injection of 40 mg flupenthixol intramuscularly
- Five days later he was readmitted due to progressively increasing stiffness of his body, difficulty in swallowing, drowsiness, and incontinence of urine
- On examination he was very rigid and semiconscious, but opened his eyes to deep pain, and had severe diaphoresis which drenched the bed clothes. However, he had no rise in body temperature. His heart rate was 130 bpm, respiratory rate 28 per minute, and his blood pressure showed marked fluctuations

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Neuroleptic malignant syndrome without fever: a report of three cases (Case-2)

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- The CPK on day-2 was 2109 IU/L and the WBC count was 12,400/mm^3 (N = 93%). Other investigations & CSF were normal. A tentative diagnosis of NMS was considered, even though the patient was afebrile, as we had patient with NMS presenting without fever previously
- The neuroleptic medication were stopped and he was started on 2.5 mg bromocriptine TDS. As the response was poor the dose was gradually increased to 10 mg TDS
- He recovered slowly and came out of the comatose state after 1 week of treatment and autonomic disturbances and rigidity disappeared after 10 days of treatment. On discharge from hospital on the day-14 after starting bromocriptine his CPK was 230 IU/L

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Neuroleptic malignant syndrome without fever: a report of three cases (Case-3)

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- An 18, boy, with schizophrenia on long term antipsychotic drugs was admitted with increasing stiffness of the body, drowsiness, and urinary incontinence
- On examination he was rigid, had tachycardia (pulse 130 bpm) alternating with bradycardia (pulse 50 bpm) and his blood pressure showed wide fluctuations
- There was no increase in body temperature at admission or during the course

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Neuroleptic malignant syndrome without fever: a report of three cases (Case-3)

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- The CPK was 1450 IU/l on the 2nd day of his illness and the white cell count was 15000/mm3 (N = 85%)
- Antipsychotic medication was stopped and he was started on 2.5 mg bromocriptine TDS He made a complete recovery, with the autonomic disturbances and rigidity subsiding within 5 days of treatment
- One week later his CPK was 100 IU/L

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Neuroleptic malignant syndrome without fever: a report of three cases

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- The NMS usually occurs with the use of therapeutic doses of neuroleptic drugs and commonly develops during the initial phases of treatment, when the drug dose is being stepped up, or when a second drug is introduced
- However, it can occur at any time during long term neuroleptic treatment with factors such as exhaustion, agitation, and dehydration acting as triggers
- There are no specific laboratory findings, but neutrophil leucocytosis and raised CPK lend weight to the diagnosis

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Neuroleptic malignant syndrome without fever: a report of three cases

(D T S PEIRIS et al, J Neurol Neurosurg Psychiatry 2000;69:277-278)

- These 3 cases illustrate the point that NMS can occur without fever
- Patients had all the features of NMS apart from fever and the response to bromocriptine can be taken as strong evidence for the diagnosis
- Being familiar with this fact and different ways in which this syndrome can present plus a high degree of suspicion are important in making an early and accurate diagnosis of NMS
- In fact, the appearance of muscle rigidity and clouding of consciousness in any patient receiving antipsychotic medication should prompt clinicians to suspect NMS and immediately initiate appropriate investigation and management

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Neuroleptic Malignant Syndrome with Delayed Onset of Fever Following Risperidone Administration

(Byron Norris et al, Ann Pharmacother December 2006 vol. 40 no. 12 2260-2264)

- A 59, female, presented with progressive weakness, confusion, and disorientation 10 days after restarting risperidone 2 mg/day for BMD. She had taken risperidone for several years prior to this episode and had stopped it for approximately 3 weeks
- Risperidone was discontinued on admission. The CPK was 901 IU/L on admission and 1991 IU/L the following day. She was initially afebrile and had no muscular rigidity. Elevated temperature (38.1 °C) did not occur until day-2
- The patient was successfully treated with diazepam, bromocriptine, and dantrolene and suffered no long-term sequelae

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Diagnosis (High index of suspicion)

- Patient on neuroleptics
- Altered sensorium
- With or without rigidity (as it may develop later)
- With or without fever (as it may develop later)

Action

- Stop neuroleptics and anticholinergics
- Get urgent CPK levels done & do serial CPK levels

Levenson's criteria for the diagnosis of NMS

(Presence of 3 major or two major and four minor signs indicate a high probability of NMS)

Major Criteria	Minor Criteria
Fever	Tachycardia
Rigidity	Abnormal Blood Pressure (BP)
Elevated CPK	Altered sensorium
	Diaphoresis
	Leucocytosis

J Anaesthesiol Clin Pharmacol. 2012 Oct-Dec; 28(4): 517–519.

A rare case of neuroleptic malignant syndrome without elevated serum CPK

(Koichi Nisijima & Katutoshi Shioda, Neuropsychiatr Dis Treat. 2014; 10: 403–407)

- Although there is no specific investigation for NMS, serum CPK elevation has been reported in over 90% of NMS patients
- In this report, we describe a patient who developed NMS but had normal CPK levels
- The patient presented with hyperthermia of over 38°C, severe muscle rigidity, autonomic dysfunction, and altered mental status.
- Although serum CPK levels were measured three times during the course of NMS, the levels were within the normal range

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A rare case of neuroleptic malignant syndrome without elevated serum CPK

(Koichi Nisijima & Katutoshi Shioda, Neuropsychiatr Dis Treat. 2014; 10: 403–407)

- The patient died of respiratory failure 13 days after the onset of NMS symptoms. As patients without elevated serum CPK levels are rarely reported, we discuss potential reasons why the serum CPK was not elevated in our patient
- This case shows clinicians that although serum CPK elevation is a useful indicator for the early detection of NMS, the diagnosis of NMS must be determined by clinical symptoms as otherwise, the appropriate treatment procedures for NMS may be delayed

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Neuroleptic malignant syndrome after neuroleptic discontinuation

(Amore M, Zazzeri N. Prog Neuropsychopharmacol Biol Psychiatry. 1995 Dec;19(8):1323-34)

- Neuroleptic withdrawal can cause autonomic and behavioural symptoms (nausea, vomiting, diarrhoea, diaphoresis, myalgia, anxiety, restlessness) and movement disorders (withdrawal emergent parkinsonism, withdrawal dyskinesia, covert dyskinesia).
- Neuroleptic malignant syndrome (NMS) is a rare but extremely severe adverse reaction to neuroleptic drugs characterized by extrapyramidal and autonomic symptoms, altered level of consciousness and abnormal laboratory findings.

Neuroleptic malignant syndrome after neuroleptic discontinuation

(Amore M, Zazzeri N. Prog Neuropsychopharmacol Biol Psychiatry. 1995 Dec;19(8):1323-34)

- Withdrawal neuroleptic malignant syndrome, though an even rarer condition (only 7 cases reported to date), should alert to consider the possibility that abrupt neuroleptic discontinuation can be complicated by NMS.
- The pathophysiology of withdrawal medical symptoms may be related to a cholinergic rebound; withdrawal neuroleptic malignant syndrome may be attributed to an "imbalance" in the dopaminergic system.
- The authors report two cases of NMS precipitated by the abrupt withdrawal of neuroleptic drugs.

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Neuroleptic malignant syndrome and clozapine withdrawal at the same time?

(Margetić B, Aukst-Margetić B. Prog Neuropsychopharmacol Biol Psychiatry. 2005 Jan;29(1):145-7.)

- The authors report a case of a patient, who in a few days after an abrupt discontinuation of clozapine and haloperidol developed agitated and confused state resembling neuroleptic malignant syndrome (NMS) and clozapine withdrawal symptoms at the same time.
- Data obtained from family members led to gradual reintroduction of clozapine and to subsequent recovery.
- The case illustrates the importance for clinicians to be familiar with the variety of discontinuation symptoms, so they can recognize them and offer effective treatment.

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Is the predisposition to neuroleptic malignant syndrome genetically transmitted?

(Otani K, et al. Br J Psychiatry. 1991 Jun;158:850-3.)

- A Japanese family consisting of a mother and her two daughters, all experienced NMS on therapeutic or sub-therapeutic doses of neuroleptics.
- The mother and the elder daughter had past histories of severe neuroleptic-induced extrapyramidal symptoms.
- The predisposition to this syndrome may be genetically transmitted. We suggest that neuroleptic treatment should be introduced with extreme caution to a patient with a family history of NMS.

Risk Factors for NMS

- Elderly People
- Genetic predisposition
- Physical exhaustion
- Warm, humid climate
- Dehydration
- More potent neuroleptics, depot preparations and higher dose

An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method

Participants:

- 11 Psychiatrists
- 2 Neurologists
- 2 Anaesthesiologists
- 2 Emergency medicine specialists

(Gurrera RJ et al. J Clin Psychiatry. 2011 Sep;72(9):1222-8)

An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method

Criteria

- Recent dopamine antagonist exposure, or dopamine agonist withdrawal
- Hyperthermia; : hyperthermia, > 100.4°F or > 38.0°C on at least 2 occasions
- Rigidity
- Mental status alteration
- CPK: at least 4 times the upper limit of normal

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An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method

Sympathetic nervous system lability:

- BP elevation, ≥ 25% above baseline
- BP fluctuation, ≥ 20 mm Hg (diastolic) or ≥ 25 mm Hg (systolic) change within 24 hours
- Tachycardia ≥ 25% above baseline; and Tachypnea, ≥ 50% above baseline
- A negative work-up for other causes

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NMS with fever

- A 40-year-old male, a case of schizophrenia on APDs
- Developed fever 100°C which within minutes increased to 106°C associated with altered sensorium and fluctuations in pulse and blood pressure
- Patient was shifted to ICU where he was there for almost 3 months
- Patient developed severe rigidity on the next day
- His CPK levels increased from around 900 to 5000 to 15,000 to 40,000 over 5 days

NMS with fever

During the course in ICU ..

- Patient developed severe dehydration and hypotension
- Patient also developed myoglobinuria (Coca Cola colour urine) and subsequent acute renal failure
- Patient also had ARDS (acute respiratory distress syndrome) and a cardiac arrest during the course

NMS with fever

Challenges:

- Management of hyperthermia
- Management of hypotension and dehydration
- Management of severe rigidity
- Management of complications – ARDS and Cardiac arrest
- Management of other complications like bed sores, pneumonia, septicaemia

Management of hyperthermia

- Tepid sponging, ice packs, ice water enema
- Antipyretics:
  - Meftal Forte (Mefenamic Acid (450) + Paracetamol (500))
  - Intramuscular diclofenac (25 mg/ml – 3 ml Amp.)
  - Intravenous paracetamol (150 mg/ml – 2 ml Amp.)
- It may take about 2-3 days for the temperature to normalize

Management of hypotension and dehydration

- Central line
- IV fluids
- Injection Mephentermine (Mephentine 15 mg)
- Dopamine drip
- Noradrenaline drip

Management of severe rigidity

- Tablet Bromocriptine (2.5 mg) 1 – 1 – 1

  Gradually increase to 4 – 4 – 4
- Tablet Amantadine (100 mg) 1 – 1 - 1
- Dantrolene sodium – not available in India
- Consider using Tablet Baclofen (30 mg) 1 – 1 -1

Management of myoglobinuria leading to acute renal shut down

- Plenty of IV fluid to flush the kidney (Vigorous hydration)
- Isotonic saline boluses of 20 mL/kg should be initially administered, with repeat boluses depending on the hydration status of the patient
- This should be followed by continued hydration with IV fluids given at a rate of 2-3 times maintenance
- Maintain blood pressure (avoid hypotension)

Management of myoglobinuria leading to acute renal shut down

- Achievement of a urine output goal of 2-3 mL/kg/h is recommended
- IV hydration should be continued until the CPK level is consistently less than 1000 U/L, the urine clears, and the patient is able to maintain adequate oral hydration

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Management of myoglobinuria leading to acute renal shut down

- Follow-up with mannitol to induce diuresis, supported by adequate IV fluids, has been advocated
- Mannitol causes diuresis, which minimizes intratubular myoglobin deposition, acts as a free radical scavenger and reduces tubule cell damage, and may act as a direct renal vasodilator
- However, the clinical benefit of this therapy remains unproven
- In retrospective studies, volume expansion with saline alone prevented acute renal failure, and mannitol had no additional benefit

Management of myoglobinuria leading to acute renal shut down

- Raising the pH of the urine to 6.5 or more can be facilitated by adding sodium bicarbonate to the fluids
- Alkalinisation of the urine has been postulated to minimize the breakdown of myoglobin into its nephrotoxic metabolites and to reduce crystallization of uric acid, thereby decreasing damage to tubule cells

Management of myoglobinuria leading to acute renal shut down

- However, this modality of therapy remains somewhat controversial because large volumes of crystalloid alone may be sufficient to alkalinize the urine and because bicarbonate therapy can aggravate the hypocalcaemia
- No large randomized trials have demonstrated that alkalinisation of urine is superior to early aggressive hydration with crystalloid in the management of rhabdomyolysis

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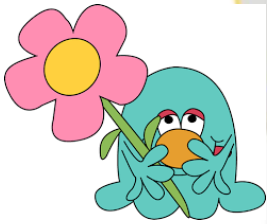
Management of complications – ARDS and Cardiac arrest

- The patient may have to be on assisted ventilation and may require cardiorespiratory resuscitation

Management of other complications like bed sores, pneumonia, septicaemia

- A good nursing care, a sterile precautions and may be prophylactic course of antibiotics may prevent these complications

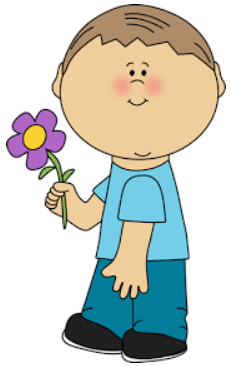


Management of vomiting

- Ondansetron (Serotonin antagonist)

Benign elevation of CPK

- 20-year-old, male, a case of schizophrenia on Risperidone has persistent elevation of CPK (around 6000 IU) without any rigidity, fever, altered sensorium and autonomic disturbances
- On withholding the antipsychotics, the CPK declines and comes down to less than 100 IU. But once the antipsychotic medications are started the CPK starts rising and reaches up to 6000 IU.



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