Neuroleptic malignant syndrome and closed head injury: A case report and review

Nissar Shaikh, Ghanem Al-Sulaiti, Abdel Nasser, Muhammad Ataur Rahman
Departments of Anesthesia/ICU, and ‘Neurosurgery, Hamad Medical Corporation, Doha-Qatar

ABSTRACT

Neuroleptic malignant syndrome (NMS) is a rare, but potentially lethal neurological emergency. Fifty percent of traumatic brain injury (TBI) patients will have emotional disorders and post-traumatic agitations. Haloperidol is a neuroleptic antipsychotic medication commonly used in the traumatic brain injury patients due to its advantage of no effect on respiration and conscious level. But it is one of the common medications causing NMS. A 19-year-old male driver involved in the road traffic accident had an acute subdural hematoma, which was immediately evacuated. Postoperatively, he was awake. He was weaned from ventilator and extubated. He received 20 mg of intravenous haloperidol in divided doses within 24 hours to control his agitation. Next day, he became drowsy, spastic, febrile, and tachycardic with labile blood pressure. He was diagnosed to have NMS, needed intubation, aggressive hydration and pharmacological treatment with dantrolene sodium and bromocriptin. He was weaned from ventilator and extubated on day 17. He was transferred to the ward and then discharged to be followed in out-patient clinic. NMS in head injury patient is rare and difficult to diagnose. Diagnosis of NMS should be suspected if two of the four cardinal signs and symptoms are developed following the use of neuroleptic or dopamine agonist medication withdrawal.

Key words: Head injury, neuroleptic malignant syndrome, neuroleptics

Introduction

Neuroleptic malignant syndrome (NMS) is ostensibly rare, but potentially lethal neurological emergency. NMS is characterized by mental status changes, muscle rigidity, hyperthermia, autonomic dysfunction, leukocytosis, and raised serum creatinine phosphokinase levels. The diagnosis of NMS in head injury patients is difficult, as these patients had neurological changes. NMS if not diagnosed early and treated properly can lead to increased morbidity and mortality. We report a case of NMS in closed head injury patient which was successfully treated in our intensive care unit.

Case Report

A 19-year-old male driver involved in the road traffic accident, brought to emergency department with head injury and Glasgow coma score of 6. Skeletal survey revealed fracture humerus. Immediately resuscitated, intubated. Computerized tomography (CT) showed subdural hematoma and underwent craniotomy and evacuation of the hematoma, postoperatively shifted to the surgical intensive care unit (SICU). His neurological status improved, weaned, and extubated on day 5. He was restless but obeying commands. He was transferred to the ward on day 7.

In ward for his agitation, he had received intravenous haloperidol 20 mg in divided doses over 24 hours. On day 10, he became highly febrile (39°C), spastic and Glasgow Coma Score (GCS) decreased to 10, and had leukocytosis (23×10^3/mm^3). CT brain did not show any new changes with the working diagnosis of meningitis; he was started on antibiotics, shifted back to SICU. His neurological status improved, weaned, and extubated on day 5. He was restless but obeying commands. He was transferred to the ward on day 7.

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Address for correspondence:
Dr. Nissar Shaikh, Department of Anesthesia/ICU, Hamad Medical Corporation, Doha-Qatar. E-mail: nissatfirdous99@gmail.com
aggressive pharmacological and surface cooling measure, added dentrolene sodium 3 mg/Kg/intravenous every 8 hours and bromocriptin 2.5 mg twice daily through nasogastric tube. On day 13, he became less restless, less febrile, and tachycardic and blood pressure became more stable. By day 15, he started to obey simple commands, fever subsided. Weaned and extubated on day 17. He was afebrile, no more spasticity and he was fully awake. Dentrolene sodium was stopped on day 18. He was transferred to the ward on day 20. On day 28, he underwent open reduction and internal fixation of fracture humerus. All standard precautions were taken for the possibility of malignant hyperthermia. He had no any perioperative complications. Bromocriptin was stopped on day 31. He was discharged home on day 33, to be followed in out patient clinics.

Discussion

NMS was first described in French literature as ‘syndrome malin’.[2] NMS is a hypodopamenergic state due to the neuroleptic medications causing severe rigidity, fever, autonomic dysfunction, and altered mental status. Millions of people all over the world suffer traumatic brain injury and up to 50% of these patients will suffer from emotional disorders and post-traumatic agitations. The pharmacological treatments of these emotional liabilities are benzodiazepines, antipsychotic, antidepressant, and beta-blockers.[3]

Haloperidol is a typical neuroleptic antipsychotic medication commonly used in the traumatic brain injury patients due to its advantage of no effect on respiration and conscious level. But it is one of the common medications causing NMS.[4]

Epidemiology

Literature about NMS associated with head injury patients is limited to the case reports only. Total nine cases of NMS are reported with use of haloperidol [Table 1] in the traumatic brain injury patients.[2,5-11] Younger patients are at higher risk for the development of NMS, it is twice more common in male, the reported incidence of NMS with use of haloperidol is ranging from 0.02 to 12.2%.[4]

| Table 1: Reported neuroleptic malignant syndrome in head injury patients |
|---------------------------------------------------------------|
| Gender | Age (Years) | Diagnosis | Reference |
|--------|-------------|-----------|-----------|
| Male   | 22          | RTA, multiple fracture skull bone, SAH | Vincent et al[2] |
| Male   | 25          | RTA, closed head injury | Heird et al[6] |
| Female | 33          | RTA, multiple brain contusion, SAH | Hirst et al[8] |
| Male   | 17          | RTA, skull fracture, SDH | Perez-Vela et al[9] |
| Male   | 38          | RTA, closed head injury | Burke et al[10] |
| Male   | 16          | RTA, midbrain contusion, intraventricular hemorrhage | Wilkinson et al[11] |
| Female | 15          | Fall from height, closed head injury | Trasmonte et al[12] |
| Male   | 22          | Fall from height, SDH, multiple brain contusions | Kadyan et al[13] |
| Male   | 21          | Fall from height, hemorrhage | Kadyan et al[14] |

RTA – Road traffic accident; SAH – Subarachnoid hemorrhage; SDH – Subdural hematoma

Risk factors

The main risk factors for the development of NMS are[12]
(i) high doses of neuroleptics (ii) rapid increase in dose of neuroleptics (iii) parental neuroleptics (iv) use of highly potent neuroleptics (v) preexisting central nervous system disorders (vi) dehydration (vii) young patients (viii) history of NMS (ix) concomitant use of predisposing medications (lithium) (x) acute medical and surgical illness (infection, trauma and surgery) (xi) anti-Parkinsonism medication withdrawal. Recently, a case is reported where high protein enteral feeding causing decreased levodopa (anti-Parkinsonism medication) concentration leading to NMS or neuroleptic malignant like syndrome.[13]

Pathophysiology

NMS is a hypodopaminergic state of the brain. Dopamine has a major role in autonomic cardiovascular stability, hypothalamic temperature regulation, maintaining the conscious level, and normal muscle tone. NMS results of either altered dopaminergic transmission or blockade of dopaminergic pathway or changes in pre/post synaptic dopamine signal activity. Neuroleptic causes blocked of the dopamine receptors, adding to it the traumatic brain (TBI) injury patients, due to diffuse axonal injury had a decreased dopamine neurotransmission. This combine effect leads to hypodopaminergic state and causing signs and symptoms of NMS.[11]

Evidence of central dopaminergic mechanism is drawn from the idea that 95% of NMS patients develop Parkinsonian symptoms. The muscular dysfunction (spasticity) with hyperthermia invokes the clinical similarity to the malignant hyperthermia. Plasma and urinary catecholamines changes in NMS patient’s supports the involvement of sympathetic nervous system. Central dopaminergic blocked or hypodopaminergic condition in hypothalamus leads to hyperthermia, where as interference with nigrostratal dopaminergic pathway causes Parkinsonian symptoms (rigidity and tremors).

The involvement of peripheral muscular system in NMS patients is either due to rigidity or direct changes in the muscle mitochondrial functions, as a result of direct toxic
effect of neuroleptic on skeletal muscles.\[^9\] The primary role played by sympathetic nervous system dysfunction also may lead to increased muscle metabolism, labile blood pressure, tachycardia, and ineffective heat loss. Familial clusters of NMS suggestive of genetic predisposition, presence of specific allele of dopamine (D2) receptor gene is over represented in NMS.\[^10\] Recently, the imaging study revealed that selective cerebellum and basal ganglia injury occurs in NMS patients.\[^11\]

**Diagnosis**

Diagnosis of NMS in patient with TBI is a tough job, as these patients common to have disturbed conscious level, fever, increased CPK due to associated blunt trauma. Diagnosis of NMS will need high index of suspicion with history of receiving neuroleptic medications and same time rule-out sepsis, worsening brain injury or meningitis.

In NMS patients, there will be history of recent administration of neuroleptic medications and disturbance of the conscious level, fever, diaphoresis, autonomic dysfunction manifested by tachycardia and labile blood pressure, lead-pipe rigidity, and tremors.

The laboratory work-up will show raised CPK, leukocytosis and increased level of hepatic transaminase, but these are nonspecific.\[^12\] CPK typically more than 1000 IU/liter and it correlates with the degree of rigidity. Serum electrolytes, coagulation profile, serum myoglobin, and complete blood count are important to be known. Cerebrospinal fluid examination and radiological scan of the brain will rule-out sepsis, worsening brain injury or meningitis. NMS develops following initiation or increased dose of neuroleptic medications, but it can occur at any time of neuroleptic therapy even after few months, 90% of NMS cases had rhabdomyolysis, aggressive fluid resuscitation with forced diuresis will be needed; these patients may have renal failure which will require renal replacement therapy.\[^13\]

Maintenance of hemodynamic is also an important aspect of management of NMS patients. Clonidine will be effective in NMS patients with tachycardia, hypertension, and restlessness.\[^14\] NMS patients with arrhythmia will need antiarrhythmic medications even the pace maker may be indicated. The medication therapy starts with stopping of the causative or precipitating medications and immediate resumption of dopaminergic medications. Most commonly used medications in the treatment of NMS are dentrolene sodium and bromocriptin. Dentrolene sodium is a direct skeletal muscle relaxant, typical daily dose is one to three mg intravenous and the maximum dose is 10 mg/kg/day. Its action starts with in minutes of administration and causes

**Differential diagnosis**

Detail medical and drug history from the relatives or patients file is of vital importance in differentiating the following conditions from NMS (1) NMS should be differentiated from serotonin syndrome [Table 2]; in serotonin syndrome patient will have history of serotonin agonist intake, these patients are hyper reactive and usually serotonin syndrome resolves within 24 hours;\[^15\] (2) Malignant hyperthermia, commonly associate and immediate to occur after the use of depolarizing muscle relaxant or inhalational anesthetics; (3) Heat stroke, history of exposed to high temperature will differentiate it from NMS; (4) Central anticholinergic syndrome, it is associated with the use of anticholinergic medications; (5) Malignant catatonia; (6) Adverse interaction of monoamine oxidase inhibitors; and (7) Central nervous system infections.\[^16\]

**Treatment**

Apart from early diagnosis, the aggressive medical treatment in intensive care set-up is essential for better outcome of these NMS patients. Stopping the causative neuroleptic is the primary step. Aggressive treatment of dehydration, electrolyte imbalance, and pharmacological or surface cooling for body temperature control is an important aspect of the therapy. Some of these patients will require airway protection and ventilatory support. If patient had rhabdomyolysis, aggressive fluid resuscitation with forced diuresis will be needed; these patients may have renal failure which will require renal replacement therapy.\[^17\]

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|**Table 2: Differences between serotonin syndrome and Neuroleptic malignant syndrome** |

| Neuromuscular finding | Serotonin Syndrome | Neuroleptic malignant syndrome |
|-----------------------|--------------------|--------------------------------|
| Causative             | Hyper reactivity   | Muscle rigidity bradykinesia   |
| Treat agent           | Serotonin agonist  | Dopamine antagonist            |
| Resolution            | Cyproheptadine     | Bromocriptine                  |
|                       | Within 24/hours    | Days to weeks                  |
Successful treatment of a complicated case of neuroleptic system infections. Treatment of NMS patients starts with central anticholinergic syndrome, and central nervous serotonin syndrome, malignant hyperthermia, heat stroke, disorders) following the use of neuroleptic or dopamine symptoms are developed (neurological deterioration, should be suspected if two of the four cardinal signs and time for complete recovery will be reduced. This medication therapy will also improve the outcome in these patients. Electroconvulsive therapy (ECT) is required in NMS patients with catatonia, patients not responding to the medical therapy. The cardiovascular complications and requirement of general anesthetics are the safety concerns with ECT therapy. Standard precautions for these concerns should be taken during the ECT therapy.[23]

Complications
NMS can be complicated with rhabdomyolysis, renal failure, seizures, respiratory failure, aspiration pneumonia, arrhythmia, residual catatonia, myopathic contractures, and decompensation of the psychiatric disease result of withdrawal of neuroleptics.[22] NMS patients can develop extensive deep venous thrombosis despite of being on thromboprophylaxis.[24]

Prognosis
NMS patients usually recover with in two weeks; the reported is ranging from 3 to 35%.[16] The mortality is high in critical ill patients and patients developing the complications such as renal failure. None of the cases reported NMS in head injury patients had mortality.[4] Higher levels of CPK in these patients indicate the severity of the disease and correlate with the higher mortality. Dextrotole and bromocriptin therapy will reduce the morbidity and mortality in NMS patients. [4]

Recommendations and Conclusion
NMS is a rare life threatening neurological emergency associated with the use of neuroleptic medications. Only nine cases of NMS in TBI patients are reported in the literature. The early diagnosis and management will have higher mortality. NMS patients with aspiration pneumonia, rhabdomyolysis, and acute renal failure will have significant higher mortality.

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