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A Review on Neuroleptic Malignant Syndrome and Its Treatment Strategy: For Clinicians

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Abstract

Neuroleptic malignant syndrome (NMS) is one of the serious complications of antipsychotics that occur rarely. Its prevalence is more commonly seen in individuals of age 20 to 40 years. Major etiology includes depletion of dopamine levels in central nervous system (CNS). It usually occurs, when high doses of antipsychotics are administered or sudden change in doses of antipsychotics or any withdrawal of anticholinergics abruptly. Sometimes, NMS follows withdrawal of dopaminergic medication in Parkinson's patients. It is characterized by 'lead pipe' muscle rigidity, autonomic dysfunction, hyperthermia, extra pyramidal side effects. Clinical manifestations of NMS resemble malignant hyperthermia, serotonin syndrome, lethal catatonia and infectious disorders of CNS. NMS is a diagnosis of exclusion, thus differential diagnosis is of utmost important, by an expertise clinician. Laboratory findings that help in diagnosis are creatine phosphokinase (CPK) levels, leukocyte count, myoglobinuria and liver enzymes. Most lethal complication constitutes death, due to multi organ failure which accounts 10% to 20 % of renal and cardiovascular failure. Management comprises of prompt withdrawal of offending antipsychotic agent/neuroleptic drug after diagnosis, dopaminergic agonists are administered and supportive care is provided to the subject. A prompt medical attention is required as a consequence of high mortality. Thus, the treatment options were proposed to reduce the mortality due to NMS in clinical settings.

Key words: Antipsychotics,Dopamine agonists, Malignant hyperthermia, Neuroleptic malignant syndrome, Neuroleptics.

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is arare and life threatening complicationwith antipsychotics[1-3]. It is an idiosyncratic reaction, acute and potentially fatal, whose occurrence is independent on duration of antipsychotic therapy[4,5]. In 1954, neuroleptic drugs were first introduced. Later, in 1968, Delay and Denikar firstly described NMS[6,7]. Neuroleptic malignant syndrome is derived from French "syndrome malin des neuroleptiques" [8]. It is also known to be "syndrome akinetichypertonique" [5].

Among antipsychotic medication, typical (Conventional) antipsychotics are known to have high risk of NMS occurrence. Pathogenesis includes Dopamine D2 receptor blockade in higher centers of central nervous system (CNS). Hallmarks of NMS include 'lead pipe' muscle rigidity, hyperthermia, altered mental status and autonomic instability. Muscle rigidity may lead to rhabdomyolysis and elevation in the creatine phosphokinase (CPK) levels in plasma which are vital manifestations[3,9-11].

Some researchers classified catatonia as NMS subtype which responds to Benzodiazepines (BZDs). whereas, Mathews and Aderibigbe classified NMS as "Drug induced hyperthermic catatonia", a subtype of catatonia and Tsai et al., categorized NMS and catatonia in the similar "Neuroleptic toxicity spectrum" [12].

We reviewed various case reports and articles published, regarding NMS, in Medscape, Science direct and Elsevier. In this article, our main aim is to provide a meticulous guide for the clinicians and pharmacists regarding the risk factors, various syndromes that are to be excluded in diagnosis and prompt management of NMS to keep mortality rates low. We mainly stressed on the history collection, early identification and aggressive pharmacotherapy. Our objective is also to indicate that a reduction in mortality rate for decades was due to early recognition and aggressive therapeutic interventions. Here, we haveprovided available treatment options to prevent death from NMS in clinical settings.

EPIDEMIOLOGY

NMS accounts for only 0.2% of psychiatric patients.[12]Incidence of NMS has been reported mostfrequently in young and middle aged adults, especially in male psychiatric patients, among whom neuroleptic use is the highest. Incidence follows downgrade in reporting [9] among patients who were on antipsychotic regimen (once incidence is as high as 3 % recently reduced to 0.01-0.02%). This reduced frequency reflects improved awareness on NMS, conservative prescribing pattern and use of atypical antipsychotics, instead of typical antipsychotics[13].

The mortality rate was 40% before 1984 for NMS, which has been declined (approx. 10%) in the recent years because of early recognition and better therapeutic agents in the treatment regimen[4,14,15]. Mortality rate without specific treatment was approximately 21% for NMS. Prevalence of NMS in patients under treatment with neuroleptic drugs ranges between 0.02% and 2.4% annually[16]. Among various case reports, young adult males were more predominant for NMS, though all age groups and both gender are affected[14].

CLINICAL MANIFESTATIONS

Clinical manifestations of NMS include muscle rigidity, hyperthermia, sweating, akinesia, dystonia, mutism, obtundation, agitation, increased pulse, altered sensorium, and blood pressure.[5] Early manifestation of imminent NMS is development of muscle rigidity followed by hyperthermia, altered mental status, and autonomic instability[3,4,17]. An elevation of WBC, myoglobin level in blood, hypokalemia and hyponatremia may also occur[40]. The core temperature in NMS patients usually ranges from 101.3 °F - 107.6 °F (38.5 °C-42 °C). Hyperthermia may precipitate direct thermal injury to Purkinje cells and may result in increased intracranial pressure lead to cerebral ischaemia combined with autonomic dysfunction[18].Mental status changes ranges from mild confusion and delirium to lethargy, stupor and coma. Manifestations due to autonomic instability are tachycardia, diaphoresis, sialorrhea, tachypnea, labile blood pressure, dysrhythmia and incontinence[4,19]. Muscle rigidity was associated with varying degree of myonecrosis and rhabdomyolysis[4]. NMS symptoms typically occur over a period of 24-72 hrs, but the risk lasts for 10-20 days after the discontinuation of oral neuroleptics and even longer for depot forms[9,14].The mean recovery time may ranges from 7-10 days[10,13].

NMS symptoms resemble various other medical conditions such as serotonin syndrome, catatonia[9], CNS infections, agitated delirium and benign extra pyramidal symptoms[13]. Clinical manifestations also resemble with malignant hyperthermia and environmental heat disorder. NMS can develop either with initiation of neuroleptic therapy or sudden dose escalation.[4] In children who were exposed to typical and atypical antipsychotics, common symptoms of NMS constitute fever, rigidity, tachycardia, and altered mental status. Time of onset ranges from immediately to 59 days. Numerous cases of NMS in childrenwho were on typical antipsychotic medication resulting death; where incase of atypical antipsychotics had a complete recovery[20]. Though many cases of NMS have been reported from decades, the clinical features still remain controversial[7].

RISK FACTORS

Usage of antipsychotic medication was considered as the major risk factor for NMS, especially the typical antipsychotics. High potency typical antipsychotics were at greater risk of precipitating NMS compared with low potency agents and atypical antipsychotics, although cases of NMS have been reported with Olanzapine, Risperidone that meet the criteria of DSM –IV[21,23]. Many case reports have been reported with haloperidol,[22,23] a typical antipsychotic that have high risk to trigger NMS even at low dose.Risk factors for developing NMS also include dehydration, depot neuroleptics, male gender of younger age[40],elderly, lack of proper management of extrapyramidal symptoms induced by neuroleptics or those which are treatment resistant, alcohol abuse, history of brain injury, catatonic symptoms and iron deficiency[42], disparity in genes that code for metabolic enzymes,[58]dopamine antagonists, abrupt cessation of dopamine agonists, rapid dose escalation of neuroleptics[8] and concurrent use of trigger medications.[9]Some studies report more cases are between 20-50 yrs age who are associated with high use of antipsychotic dosage forms[44]. Polymorphism of CYP450 enzyme is also a pharmacogenetic risk factor[40].Antidopaminergic properties of antipsychotics may lead to NMS, which is reinforced by disorders counter to dopamine agonists like bromocriptine[43].Metoclopromide, an anti-emetic having dopamine blocking property may increase the risk of NMS along with drugs such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antiepileptics[55] and lithium[24] when administered concomitantly with neuroleptics[8,25,26]. List of drugs of various classes that can increase the risk of precipitating NMS are shown in Table 1.

Abrupt cessation of neuroleptics in any patient, who was on long term treatment for psychiatric disorder, was also at increased risk for developing NMS[14,27]. Several clinical, systemic and metabolic risk factors that may precipitate NMS include agitation, dehydration[5], and restraint, abnormality in CNS dopamine activity, thyrotoxicosis and iron deficiency. Patients with catatonia on antipsychotics were at high risk of progressing to this syndrome. In various cases, dehydration prior to NMS onset has been reported[13]. As dehydration and nutritional disorders are risk factors, patients with early post-partum period were also at high risk of precipitating NMS[8,28].

Concomitant diseases that may precipitate NMS include Acquired immunodeficiency syndrome AIDS-related dementia, head trauma, organic brain diseases[4], delirium, sympathoadrenal hyperactivity[14], encephalitis, tumor in brain[17]. Depot forms, high dose of neuroleptics, high ambient temperatures and humidity and substances of abuse (e.g.: alcohol) were also associated with an increased risk; but there was a significant number of NMS cases have been reported at therapeutic doses of antipsychotics[8,13,14]. Table 2 provides a detailed note on the predisposing factors in NMS patients as risk factors.

Prior to Deep Brain Stimulation (DBS), discontinuation of antiparkinsons medication is the common practice that may trigger an episode. DBS activation may accelerate the patient's recovery[29].

PATHOPHYSIOLOGY

Pathophysiology of NMS is more complex and the precise mechanisms are still unproven. It likely involves blockade of hypothalamic and nigrostriatal dopaminergic pathways and of peripheral neuromuscular system. Central dopaminergic blockade elucidates the clinical symptoms seen during theepisode of NMS. Blockade in corpus striatum results in muscle contraction and rigidity which subsequently leads to impairment of heat-dissipating mechanisms, resulting in hyperthermia. Hyperthermia can also occur when dopaminergic receptors blockade occur in thermoregulatory centers of the pre optic nuclei of the anterior hypothalamus. Dopamine receptor blockade in the nigrostriatal pathway and spinal cord results in altered mental status and autonomic dysfunction respectively[4,14,30]. Pathogenesis involving cascade of dysregulation in multiple neurochemical and neuroendocrine systems finally lead to a hyper metabolic syndrome. This

hypothesis is supported by: (i) Withdrawal of dopamine agonists and administration of dopamine receptor blockade agents can precipitate NMS (ii) NMS symptoms are relieved by dopaminergic drugs and (iii) Patients with central dopamine tract lesions are at high risk of developing syndromes that contribute many clinical characteristics with NMS. Disparity in serotonergic neurotransmission and excess of central serotonin causes a hypodopaminergic state which is another risk factor for NMS. Inadequacy in calcium regulative proteins and removal of tonic hindrance in the sympathetic nervous system also plays a significant role in the pathogenesis of NMS[42]. In patients with acute NMS, dopamine metabolite homovanillic acid concentrations in CSF is low that supports the central role of dopaminergic hypo function. The cascade of autonomic dysfunction, rise in catecholamine levels in many cases and sympathoadrenal dysfunction have contributing role in developing this syndrome.[13] In patients, who have recovered from symptoms have searched for dopamine 2 receptor gene polymorphism, although results have not been rational[31].

Most preferred hypothesis for pathogenesis of NMS due to neuroleptic drugs involves depletion of dopamine levels or blockade of dopaminergic receptors in various areas of CNS including- hypothalamus, corpus striatum, basal ganglion and spinal areas[4]. Another system which plays a role in developing signs and symptoms of NMS is the peripheral skeletal muscle system. Consequent to antipsychotics usage, there is an elevation in the calcium release from sarcoplasmic reticulum of muscle cells possibly leading to muscle contractility and rigidity, rhabdomyolysis and hyperthermia[8,17].

There is also a hypothesis that there is an up-regulation of muscarinic acetylcholine receptors (MAchR) by long term neuroleptic therapy. Consequently, cholinergic hyperactivity is possible following abrupt withdrawal of neuroleptic agents that precipitate NMS due to hypo-dopaminergic state along with reduced anticholinergic load. The withdrawal of anticholinergic agents can provoke hyper-cholinergic rebound state that can also precipitate NMS[27]. Recent studies imply that proinflammatory cytokines released by activated macrophages could add to pathogenesis of NMS. Macrophage infiltration and acute inflammation is a feature of pathology of acute disseminated encephalomyelitis(ADEM) and basal ganglia involvement. Occurrence of NMS in ADEM is uncommon[45].

DIAGNOSIS

For diagnosing NMS, various criteria have been proposed including Levenson[10], Pope et al., Caroff and the DSM-V. Collecting a complete medical history and even time line is crucial in diagnosis of NMS due to its resemblance with other medical conditions that are difficult to distinguish[9,32]. NMS is a diagnosis of exclusion[4,14], because there are no consistent diagnostic criteria. Diagnostic and Statistical Manual Of Mental Disorders, Fourth Edition (DSM–IV-TR) criteria require at least two associative symptoms, which usually include severe muscle rigidity, altered mental status, diaphoresis and hyperthermia, to be present following a history of recent administration of an antipsychotic drug as well as other signs or lab investigations, that are not influenced by any other etiology[13,20].

Laboratory investigations are imperative to exclude other disorders or complications. None of the laboratory findings are specific for NMS. Even though laboratory findings are nonspecific, certain laboratory abnormalities are correlated with signs and symptoms which will aid in diagnosing NMS[4,13,14].

A complete laboratory evaluation including CPK levels, WBC count, renal function tests, serum lithium concentrations, besides taking precise history and physical examination, are essential[4,14]. In NMS patients, rhabdomyolysis results in sharp elevation in serum CPK, aldolase, transaminases, lactic acid-dehydrogenase concentrations, which finally leads to myoglobinuric[14] renal failure. Detection of these laboratory findings will provide confirmatory diagnosis[13,30].Thelack of an authoritative diagnostic test for NMS complicates its identification in intubated polytrauma patients where associated comorbidities lead to other etiologies of fever and altered mental status[40].

Amongst the laboratory findings CPK levels are of prior importance because it is elevated in nearly all cases of NMS as a result of rhabdomyolysis. Higher CPK values have been observed in cases with high cumulative neuroleptic dose during the episode of NMS[8]. However, the maximum plasma elevation of CPK is non-consistent although the behavior generally observed is elevation upto 4 times the upper normal limit[54]. CPK level measures the amount of myonecrosis and is an indicator of potential acute renal failure. In most cases, death from NMS is due to renal failure. Diagnosis of exclusion can also be carried out using investigations like Electrocardiogram, Electroencephalogram, Chest radiography, Computed tomography of head and CSF analysis, which are normal in most of NMS cases. Other non-specific laboratory findings include glucocytosis. Besides a metabolic acidosis, hypoxia, hyper or hyponatremia, azotemia, myoglobunuria and mild coagulopathies, decreased serum iron concentrations, elevated catecholamines have been seen in various case reports[4,13].In most cases, NMS develops within 30 days after initiation of antipsychotic treatment. Unless dose of antipsychotic was increased or additional antipsychotic administered, it was unusual to occur beyond 1 month. After the NMS symptoms were resolved in some patients, catatonia and Parkinsonism remained persistant for weeks. Clinicians should be aware that NMS is heterogeneous in onset, presentation, progression and outcome[13]. Even though 90% of reported cases show elevated CPK levels in serum as cardinal feature, case reports without raise in CPK values were also diagnosed as NMS. These case reports meet the diagnostic criteria proposed by Levenson, Pope et al., Caroff and Mann and DSM-IV-TR. Such cases were rarely reported in literature.[32] Similarly, leukocytosis is one of the hallmarks of NMS along with CPK elevation, a case report with normal WBC count was reported who was on Quetiapine maintenance therapy[5]. It is difficult to distinguish lithium neurotoxicity from NMS. However, fever is not seen in lithium neurotoxicity, manifestations include weakness, extreme lethargy, fasciculations, cerebellar signs, seizures and myoclonic jerks. Based on the clinical symptoms, lithium neurotoxicity can be excluded[25].Considering factors such as severity of hyperthermia, rigidity, altered mental status and elevation in serum CPK levels, rating scales have been introduced in course of NMS.[13] Physicians should bear in mind that clinical features of NMS, with atypical antipsychotics may present differently than that of typical antipsychotics. However, diagnosis of NMS must not be delayed due to atypical presentation and must be based on clinical manifestations if the diagnostic criteria of DSM-V-TR are fulfilled[54].A review of clozapine induced NMS cases did not show muscle rigidity by the subjects[33]. NMS associated with atypical

antipsychotics may not be severe as compared to typical antipsychotics[12,34].

Table 1: Drugs, as risk factor that may precipitate NMS

Class Of Drugs	Drugs
Neuroleptics	
a) Typical or Conventional	Haloperidol, Chlorpromazine
b) Atypical or Newer Generation	Olanzapine, Risperidone, Quetiapine
Dopamine Antagonists	Metoclopramide
Tricyclic Antidepressants (TCAs)	Amitriptyline, Desipramine, Amoxapine
Mono Amino Oxidase Inhibitors (MAOIs)	Phenelzine, Tranylcypromine
Selective Serotonin Reuptake Inhibitors (SSRIs)	Paroxetine, Sertraline , Fluoxetine
Anticonvulsants	Oxcarbazepine, Phenytoin
Abrupt Withdrawal Of Dopamine Agonists	Levodopa, Amantadine, Bromocriptine
Skeletal Muscle Relaxant	Carisoprodol [53]
Miscellaneous	Lithium Combination with Antipsychotics

Table 2: Risk factors that may precipitate NMS

Clinical factors	Underlying diseases	Other Predisposing factors
Agitation	AIDS	Dehydration
Restraint	Brain lesions	High potency drugs
Thyrotoxicosis	Delirium,	Neuroleptic depot forms
Iron deficiency	Encephalitis	Male sex
	Tumor in brain	Head trauma
		High ambient temperature
		Humidity Substance abuse.

Table 3: Differential Diagnosis

DISEASE	TRIGGERS
NMS	Neuroleptics
Serotonin syndrome	Serotonergic Drugs (SSRIs, TCAs, MAOIs And Triptans)
Malignant hyperthermia	Anaesthetics
Drug toxicity	Lithium, Substances abuse, Meperidine, Fenfluramine
CNS infection (Meningitis)	Infectious etiology
Convulsions	Epilepsy

In Catatonia, motor features are preceded by behavioral changes

DIFFERENTIAL DIAGNOSIS

NMS can be typically distinguished by obtaining comprehensive data on medical history, the absence of leukocytosis and elevation in CPK levels and the presence of gastrointestinal symptoms[17].Prodromal viral illnesses, meningeal signs, headaches, localizing neurological signs, CSF findings[14], seizures and neuro-imaging are ruled out to exclude infectious aetiology. Risk of extrapyramidal symptoms in NMS may be high in patients with HIV and other viruses that affect mid brain. Lesions in the midbrain and brain stem as well as non-convulsive status epilepticus can mimic NMS. Such conditions should be scrutinized to distinguish NMS. In most of the cases NMS is self-limited, after the discontinuation of offending agent. In psychiatric patients, receiving antipsychotics, NMS is difficult to differentiate when heat stroke is present with hyperthermia, confusion, tachycardia and tachypnea. However, in heat stroke, skin is dry and muscle flaccidity is commonly seen after exposure to high ambient temperatures. Serotonergic drugs which include SSRIs, TCAs, MAOIs and triptans can cause serotonin syndrome presented with agitated delirium that resembles NMS. The symptomatic features that distinguish serotonin syndrome from NMS include chills, ataxia, myoclonus, hypereflexia and patellar clonus. There is no conflicting rise of CPK and liver enzymes in SS as in NMS. Usually NMS takes longer time to emerge whereas serotonin syndrome develops within hours after exposure to triggering agents[9]. Also, most patients with SS recover within a week of the stoppage of the causative agent unlike in NMS where it takes several weeks[47]. Patients may develop malignant hyperthermia during general anesthesia that produce signs like NMS due to a primary pharmacogenetic muscle disorder which cannot be relieved by neuromuscular blocking agents. Dopamine antagonists and withdrawal of dopamine agonists or of the GABA-ergic drug Baclofen can also precipitate NMS like reaction[13,14,26]. Various drugs which trigger other syndromes that are to be differentiated are shown in Table 3. Drugs include Lithium, Meperidine and Fenfluramine at toxic levels produce NMS like symptoms. Drugs of abuse such as cocaine, amphetamine, methamphetamine, phencyclidine and 3,4-methylinedioxymethamphetamine intoxication besides alcohol withdrawal produce syndrome with hyperthermia, altered mental status and autonomic dysfunction which can be confused with NMS easily[13,17].

Catatonia is a neuropsychiatric syndrome which is distinguished by mutism, immobility, negativism, excitement, catalepsy, stupor, refusal to eat or drink, posturing and excitement or hyperkinesis. When neuroleptics are administered to catatonic patients, the dopamine blockade produced would aggravate the already meager dopaminergic activity that will lead to precipitation of NMS[48]. (Lethal catatonia, a psychiatric disorder, which is life threatening, is indistinguishable from NMS because of similar clinical features[12]. But in Catatonia motor features are preceded by behavioral changes[14, 17].) Cut it.

The diagnostic features of NMS according to DSM-V-TR criteria which include rigidity, changes in mental status, dysautonomia, elevated temperature were often found to be present in the cases of Progressive Encephalomyelitis with Rigidity and Myoclonus(PERM) in studies except with the elevation of CK[51].

NMS may also result secondary to Myxedema coma which is a life-threatening condition that represents severe hypothyroidism with physiological decompensation. The pathogenesis behind such an occurrence are the metabolic changes that occur peripheral to primary hypothyroidism resulting in elevation of dopaminergic activity in the central dopaminergic tracts making the person susceptible to the idiosyncratic reaction of NMS[52].

There have been cases where differences have been reported in the clinical presentation of NMS between atypical and typical antipsychotics. Tremors, rigidity and fever are seen only occasionally with atypical antipsychotics while diaphoresis is usual even though different drugs have varying symptom profiles. Substantial amount of cases of atypical induced NMS have been associated with risperidone. Clozapine-related agranulocytosismust be ruled out before the diagnosis of NMS in patients who present with fever and autonomic instability without rigidity[57].

COMPLICATIONS

NMS complications are of diverse in nature. The most universally occurring complication is rhabdomyolysis resulting from muscle damage. Besides, early in the course of NMS, complications include renal failure, respiratory distress syndrome, aspiration pneumonia, pulmonary edema, sepsis, embolism, intravascular coagulopathy, myocardial infarction and seizures, cardiac arrest or respiratory failure which may lead to death[4,13].

TREATMENT AND MANAGEMENT

Neuroleptic malignant syndrome requires neurologic emergency in treatment, as a delay in treatment lead to severe morbidity and death.[17]The effective management involves the prompt recognition of clinical disorders that share similar clinical features with NMS that are to be excluded and immediate withdrawal of offending drug as well as implementation of supportive care and other therapeutic interventions[4,13].

Treatment with dopamine agonists and supportive therapy cannot be excluded based on their potential benefits which have been reported in various case reports on NMS. A study evaluated that treatment with Bromocriptine or Dantrolene showed rapid recovery than supportive therapy alone[35]. Alternative therapy with Amantadine also shows successful remission of symptoms in some cases[36]. Antiparkinsonism drugs like Levodopa in combination with Carbidopa can be used to relieve extrapyramidal symptoms and hyperthermia[3, 37].Interestingly, neuroleptic agents cannot be eliminated by dialysis, thus reduction in blood concentration of drug cannot be achieved easily. Treatment should be done aggressively for NMS complications. In an immobilized patient, to prevent venous thrombosis Heparin is indicated, whereas Metoclopramide, a dopamine-antagonist, is contraindicated. Efficacy of specific treatment remains controversial, which cannot be evaluated due to lack of sufficient literature[14].

Management of NMS is usually of two types:

1. Supportive therapy
2. Pharmacological treatment

Supportive Therapy

Prior management of NMS includes cessation of offending neuroleptic medication then supportive medical therapy is the main stay of management of NMS. Supportive care includes use of cooling devices[3], fluids and electrolyte replenishment, and treatment of potential complications[4]. Nasal gases administering O2 at a FiO2 in the range of 24-28% is necessary.In extreme hyperthermia, physical cooling measures are predominant. Noninvasive cooling devices are very effective and safe to overcome hyperthermia with neither local nor systemic side effects. Most of the NMS patients are dehydrated, thus volume resuscitation should be done. Electrolyte abnormalities should be corrected and monitored sequentially. Electrolyte fluids or bicarbonate loading may be of particular benefit in preventing renal failure. Careful monitoring should be done for complications, including cardio-respiratory failure, renal failure, aspiration pneumonia and coagulopathies[13].

Pharmacological Treatment

NMS is a self-limited iatrogenic disorder. Cessation of antipsychotic medication and medical therapy may adequate to recover from symptoms. There is no evidence on specific remedies for NMS to improve outcome. Because the NMS is a rare, heterogeneous and unpredictable in onset, it is difficult to compare specific treatment for NMS[13].

Dopaminergic agents

Dopamine agonists such as Bromocriptine and Amantadine are effective[20] in treatment, as there is a fact that NMS is due to dopaminergic blockade centrally. These drugs will help in restoration of central dopaminergic balance that facilitates recovery from hazardous NMS. Amantadine is initiated at 200-400 mg/day in divided doses through orally or nasogastric tubes; whereas Bromocriptine starts with dose of 2.5 mg orally BID or TID, increased up to 45mg/day if indicated. Bromocriptine can aggravate psychosis and hypotension, monitor closely. Premature discontinuation of Bromocriptine may result in rebound symptoms. Until the symptoms resolved dopamine agonist treatment [4] should be continued. In various case reports [16] and meta-analysis, it has been reported that dopaminergic agents when used alone or in combination with other agents reduce mortality rate by halve and time to recovery[13].

In special cases, where NMS presented with emesis and achalasia, oral administration of Bromocriptine or Amantadine shows patient adherence problems. In such cases, subcutaneous administration of Apomorphine at a dose of 2 mg q3h for 3 days, and 2mg q6h for 6 days can be recommended[15].

Dantrolene

Dantrolene was initially the drug of choice for anesthesia induced malignant hyperthermia. Because of its muscle relaxant property, it is used to control major symptoms of NMS. Dantrolene may be useful in NMS cases with extreme muscle rigidity, hyperthermia and hyper-metabolism. In some meta-analysis, mono-therapy with Dantrolene has shown improvement in 80% of NMS cases have been reported. Dantrolene block the release of calcium from sarcoplasmic reticulum thus works in tandem with central dopaminergic agonist to alleviate the pyrexia symptoms peripherally. Dosing of IV Dantrolene starts with 1-2.5 mg/kg body weight followed by 1 mg/kg 6th hourly if fever and rigidity resolved rapidly, with tapering to oral form of Dantrolene. Besides, other pharmacological agents used include benzodiazepines, which synergistically act as central muscle relaxant to attenuate muscle related heat in NMS. Correspondingly reduces heart rate and respiratory rate[4,13,14].

Dantrolene can be given up to 10mg/kg/day. Beyond 10mg/kg/day dose of Dantrolene may precipitate hepatotoxicity[14,17]. If the subject has altered liver function, the use of Dantrolene is limited[18].

Benzodiazepines

Although Benzodiazepines donot have preventive effect in NMS, they may ameliorate symptoms particularly in milder cases and hasten recovery. Among benzodiazepines, Lorazepam had shown its efficacy to abate symptoms in various case reports[36, 5]. Lorazepam starts with 1-2 mg parenterally, and titrate the dose accordingly, as a first line intervention in patients with acute NMS and primarily catatonic symptoms[13]. Diazepam is used to treat symptoms of muscular rigidity, catatonia and agitation[43, 49].

Steroid Therapy

Methylprednisolone pulse therapy is seen to be effective for patients of Parkinson's disease having NMS for lessening the duration of illness and ameliorating its clinical manifestations. The enhancement of organ system manifestations of NMS is likely to occur as a result of the stabilizing effect of Methylprednisolone on lysosomal membrane. Methylprednisolone also causes enhancement of dopaminergic activity of NMS in Parkinson disease patients[56].

Electroconvulsive Therapy (ECT)

When pharmacotherapy and supportive care fail to recover the symptoms of NMS, ECT may be effective to alleviate the symptoms[12, 13, 20]. ECT is a relatively safe procedure[14] which includes 6-10 sessions- daily with bilateral electrode placement. It is necessary to maintain a minimum of 6 sessions to reduce the risk of relapse[13, 15]. Thus, cases that are unresponsive to supportive medical therapy, ECT is an effective and rapid mode of treatment for NMS[13, 14]. Continuation of BZD's therapy is beneficial in patient undergoing ECT which will accelerate recovery from episode. For severe or prolonged NMS cases, ECT is indicated with BZDs[15].

Besides its effectiveness in terms of recovery of symptoms, ECT appears to reduce mortality, so it can be indicated as second line of therapy. ECT can also be used as first-line treatment, where a lethal catatonia cannot be distinguished or where the acute NMS-related metabolic symptoms have been resolved but Parkinsonian or catatonia-like symptoms persist. When the underlying disease represents psychotic depression, ECT can be indicated for early use[15].

Treatment pattern to be followed for NMS in clinical settings

Based on our review, we proposed the treatment pattern, to be followed, for NMS in critical care to reduce the mortality rate. The pattern is as follows:

A. As soon as the patient is diagnosed with NMS, withdrawal of offending agent, usually Neuroleptics, is the primary step in treatment.
B. Patient may recover after cessation of offending agent, as discussed earlier NMS is self-limiting disorder.
C. Patient must be provided with the supportive measures.
D. If symptoms of NMS persist even after cessation of offending agent, start treatment with dopamine agonists, in the doses as indicated, aggressively. Dantrolene, a muscle relaxant can also be considered as mono therapy or in combination with BZDs or Dopamine agonists.
E. Levodopa in combination with Carbidopa can also be recommended to relieve cardinal features of NMS such as extrapyramidal symptoms and hyperthermia, particularly in Parkinsonism patients.
F. ECT is the main stay of treatment, if pharmacotherapy fails.

In Special cases

a) If NMS is associated with drugs other than Neuroleptics, especially dopamine antagonists, immediately start dopamine-agonists for better prognosis.
b) ECT is indicated along with BZDs therapy in severe or prolonged NMS cases.
c) ECT is the first line of therapy, if Parkinsonism or catatonia symptoms persist.
d) When underlying disease is depression, ECT is indicated for early use.

RECHALLENGE

Rechallenge with antipsychotics is necessary in many patients, since NMS occurs mostly in psychiatric patients who need further treatment with antipsychotics[30]. Rechallenge with neuroleptics having high potency or too quickly after preceding episode results in reoccurrence. Reoccurrence of NMS is as high as 30% with antipsychotic rechallenge after resolution of previous episode. In some case reports, successful rechallenge have been reported; neuroleptics can be safely[15] reintroduced with very slow titration and careful monitoring after a washout period of about two weeks[34] for oral neuroleptics and at least 6 weeks for a depot form. It is safer to use an alternative neuroleptic drug than the one which is associated with the development of previous episode[4, 13, 17, 36].

A preventive program had been done in the past, for 3 years, which concluded that, without reoccurrence, reintroduction of neuroleptic medication was possible after ECT in patients whom symptoms of previous episode is subsided, although neuroleptics reintroduction may result reoccurrence of NMS[38]. Safest approach to rechallenge neuroleptic is slow titration of dose and use of low potency neuroleptic medication (e.g.: Clozapine) to prevent occurrence of further NMS episode[4,14]. After rechallenge, patient should be monitored closely for NMS symptoms. Antipsychotic dechallenge and prompt treatment for NMS should start, if signs appear[4].

PROGNOSIS

"Early recognition and prompt treatment will reduce the fatal outcome from NMS", stated Caroff et al[38]. Avoidance of dehydration in NMS treated subjects will reduce the morbidity, prevalence and further occurrence of syndrome[14].Events like hyperpyrexia, rhabdomyolysis and neuronal damage may lead to amnesia which could be temporary or resistant in some cases[49]. Due to increased physician awareness, reports of mortality from NMS have been reduced. Early recognition of NMS symptoms and aggressive treatment will provide a complete recovery with-in 2-14 days[4, 13]. Unless diagnosed earlier, resolution of symptoms take several weeks or longer. If death occurs, it may be due to renal failure or respiratory failure or arrhythmias[1, 17].

SUMMARY AND RECOMMENDATIONS

NMS is rare and potentially life threatening disorder related to the administration of neuroleptics. Cardinal features include muscle rigidity followed by hyperthermia and autonomic instability. Still to date, none of the theories can explain the underlying cause of NMS that affect only small fraction of patients who are on neuroleptic medication. An expertise physician should aware of symptoms and make an accurate diagnosis by exclusion and collecting a comprehensive medical data along with complete laboratory investigations. Early recognition of symptoms and prompt treatment including cessation of neuroleptic agent, pharmacotherapy and supportive measures are crucial in recovery from episode. In severe cases, where symptoms are prolonged and cannot be relieved on pharmacotherapy, physician must give stress on ECT as therapeutic option both in terms of timing and technique. Preventive measures include conservative use of neuroleptics and prescriber should be aware of cumulative dose and prescribing high dose of medication over a prolonged duration. For rechallenge, a 2 weeks wash out period is mandatory to prevent further episode and low potency agent at dose should be started and titrated slowly in a monitoring setting with careful assessment as there are upto 30% chances of reoccurrence[50]. Its rarity, severity and fatality make impossible to conduct controlled trails. Thus, further research is required to obtain a comprehensive knowledge regarding NMS.

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