

Life-threatening conditions in psychiatry – neuroleptic malignant syndrome (NMS)

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Abstract

The introduction of neuroleptics in the 1950's was a turning point in psychiatric treatment. The new drugs brought hope to millions of patients and their doctors. However, there were also some side-effects, one of which is Neuroleptic malignant syndrome (NMS), a rare complication of antipsychotic treatment and untreated it may lead to mortality as high as 20%. The incidence of NMS, estimated to be 0.01–0.02%, has decreased significantly probably due to higher awareness of the diseases and shift to atypical antipsychotics. The aim of this study was to present the signs and symptoms of this rare condition and describe management possibilities since this condition is observed not only in psychiatric departments but also in emergency rooms. NMS is thought to be related to change caused by neuroleptics within the central nervous system due to dopamine D2 receptor antagonism, especially nigrostriatal pathways and the hypothalamus. There are three symptoms which are considered as major and indicate a high probability of NMS: muscle rigidity, hyperthermia (core body temperature above 38.5 °C), and elevated creatine phosphokinase concentration (above 1000 U/l). NMS is a diagnosis of exclusion and clinicians must be vigilant in detecting early signs of NMS. The basic management in NMS is antipsychotic discontinuation and proper supportive care of the patient (vital signs monitoring, hydration, correction of electrolyte and acid-base disturbances). In more severe cases, the introduction of bromocriptine or dantrolene, as well as benzodiazepines, may be indicated. Further usage of neuroleptic in patients with a history of NMS should be with care, and low doses of low-potency neuroleptics or atypical neuroleptics seem to be the best treatment choice.

Key words

Neuroleptic malignant syndrome, NMS, neuroleptic, muscle rigidity, hyperthermia

INTRODUCTION

Life-threatening situations in psychiatric patients who do not suffer from somatic disorders are relatively rare. One of the most dangerous among such situations is potentially fatal neuroleptic malignant syndrome (NMS) associated with use of neuroleptic drugs. Prospective studies provided some data regarding frequency of NMS which ranges from 0.07% – 2.2% of all patients receiving neuroleptics [1, 2]. According to Caroff, the lifetime frequency of NMS among patients receiving neuroleptics is 0.2%, and more recent data suggest that the incidence of NMS is 0.01–0.02%. [3, 4]. The decrease in NMS occurrence probably results from higher awareness of the disease and less often prescription of typical antipsychotics, and a shift to newer, atypical antipsychotics. Mortality in the case of unrecognized or untreated NMS is 5–20% [5, 6]. First descriptions of this syndrome were presented by Delay et al. who observed a syndrome which they called 'akinetic hypertonic syndrome' [1]. This description was introduced after 1960 when neuroleptics were introduced. Since then, about 1,000 cases of NMS have been reported, although the syndrome itself, as well as some of its features, remains a mystery. In 2011, however, Gurrera et al. reached consensus on the diagnostic criteria for NMS [7, 8]. The presented study attempts to present a short

pathophysiology of NMS, its clinical features, propositions for diagnostic criteria, risk factors, differential diagnosis, and basic treatment principles.

Pathophysiology of NMS. There are two theories which may explain NMS. First, is the neuroleptic-related change within the central nervous system due to dopamine D2 receptor antagonism, especially nigrostriatal pathways and the hypothalamus. Dopamine plays a major role in thermoregulation, and central dopamine D2 receptor blockage by neuroleptics may result in hyperthermia and impairment of thermoregulation mechanisms. This theory is supported by results of studies in which dopamine receptors agonists, such as amantadine and bromocriptine, show its efficacy in NMS treatment [1, 5]. Is it thought that central dopamine D2 receptor antagonism results in muscle rigidity and tremor which produce heat. At the same time, heat-dissipating mechanisms are deregulated by the D2 receptors blockage which, in addition to overproduction of heat, lead to development of hyperthermia as one of the main signs of NMS [1, 9]. This may lead additionally to a decrease in tonic inhibition from the sympathetic nervous system which results in sympathoadrenal hyperactivity. Therefore, patients with a high level of sympathoadrenal activity at the beginning of neuroleptic treatment are in the risk group for NMS development [10]. However, it is a well-known fact central thermoregulation involves not only dopaminergic but also serotonergic, noradrenergic and cholinergic pathways, and disturbances in the dopaminergic pathway cannot be fully responsible for development of NMS [1].

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Some features of NMS are similar to the signs and symptoms of malignant hyperthermia, which suggests that NMS may be a result of abnormal muscle reaction. These similarities involve clinical features of both disorders: hyperthermia, muscle rigidity and creatine kinase concentration elevation, as well as high mortality rates in the course of both disorders which are as high as 10–30% [11], good reaction to sodium dantrolene observed in both syndromes, as well as abnormal results of *in vitro* contractility test in patients with NMS and malignant hyperthermia [1].

Clinical presentation and diagnostic criteria. Typically, NMS signs and symptoms develop within 24–72 hours after introduction of an antipsychotic drug; however, in few cases, the development of symptoms is more insidious. The likelihood of NMS is much higher with the use of potent neuroleptics, such as haloperidol and fluphenazin. Nevertheless, NMS may develop with all types, both typical or atypical, of antipsychotic medications. There are case reports of NMS associated with prochlorperazine, promethazine, risperidone, olanzapine, aripiprazole, quetiapine, sulpiride, ziprasidone, and even clozapine [12, 13, 14, 15]. A few non-neuroleptic agents that the block central dopaminergic pathways, such as metoclopramide, amoxapine, phenytoin, tetrabenazin, rezepin, valproate [16] and lithium, may lead to NMS [5, 4]. The risk of NMS development lasts for up to 20 days, even after the suspected drug is discontinued orally, and more that 20 days when the drug is delivered in a depot form [5, 4].

Three symptoms are considered as major and indicate a high probability of NMS: muscle rigidity, hyperthermia (core body temperature above 38.5 °C and in some cases as high as 42 °C), and elevated creatine phosphokinase concentration (above 1,000 U/l, in some cases as high as 50,000 U/l).

Muscle rigidity is a first sign in more than 80% of all patients [5], and in more than 95% of all cases is described as a 'lead pipe' increase in tone. This may result in decrease of chest compliance leading to hypoventilation associated with tachypnoe creating a risk of pulmonary infection [1, 5]. In some cases, muscle rigidity is accompanied by dyskinesia, dysarthria or Parkinsonian tremor [1, 5].

An increase in core body temperature is observed in most patients in the absence of other systemic illnesses, and the rise of body temperature may be fast, up to 42 °C, and can be fatal due to renal or respiratory failure [2, 11]. Acute renal failure may also be a result of muscle necrosis due to intensive muscle contracture, which is reflected by elevated creatine phosphokinase concentration [1, 2, 11].

Besides the three major signs, a wide range of minor clinical features are also observed. Patients with NMS present signs of sympathetic nervous system dysfunction, such as tachycardia, tachypnoe, high blood pressure and diaphoresis. Their mental status is changed and they may be highly agitated or even in a coma. Other signs less frequently reported include chorea, seizures, Babinski sign, trismus and opistothonus [1, 2, 5, 7].

The most important laboratory finding is elevated creatine phosphokinase concentration; however, some other changes in laboratory results are observed, including leucocytosis (up 30,000/mm³ in some cases), elevated hepatic enzymes (alkaline phosphatase, transaminase and lactic dehydrogenase), elevated mioglobin concentration and mioglobinuria. Flattening of the EEG is also observed [5,6].

Head CT scans are normal and some authors have reported non-specific changes in muscle biopsy or *post-mortem* histopathological examinations of the brain [1, 2]. In 2011, an expert panel reached a consensus on NMS diagnostic criteria (Tab. 1) [7, 8].

Table 1. NMS diagnostic criteria [7, 8]

Exposure to dopamine agonist, or dopamine-agonist withdrawal, within the past 72 hours
Hyperthermia
Rigidity
Mental status alteration
Elevated creatine phosphokinase
Sympathetic nervous system lability, defined as the presence of two or more of these features: elevated blood pressure, blood pressure fluctuation, diaphoresis, or urinary incontinence
Tachycardia and tachypnea
Negative work-up for infectious, toxic, metabolic, and neurologic causes NMS – neuroleptic malignant syndrome.

Mortality in course of NMS usually results from myoglobinuric renal failure (a strong predictor of mortality), respiratory failure, cardiovascular collapse, arrhythmias, or DIC and may be as high as 14% for oral neuroleptics and 38% for depot forms [8, 11]. In recent years, mortality from NMS has decreased. Shalev, Hermsch and Munitz reported a significant decrease (11%) in mortality since 1984 [17]. This may result from the introduction of novel, atypical neuroleptics, increased awareness of the condition and conservative antipsychotic prescribing practices.

NMS risk factors. As mentioned above, high potency antipsychotics increase the risk of NMS development. The onset of the syndrome is not related to duration of antipsychotic treatment. Usually, NMS develops after a few weeks of treatment; however, in some case it may be recognized even after years of antipsychotic treatment [5, 6]. Abrupt discontinuation of antipsychotics or antiparkinsonian drugs have been reported to produce NMS [1].

Both genders are affected by this condition, although being a young male increases the risk for NMS, which has been described in all ages, including children. Patients who receive neuroleptics in the perioperative period or with polytrauma are more likely to develop NMS [1, 11].

Ethanol toxicity and malnutrition lead to some muscle abnormalities; thus, alcoholic patients who receive antipsychotics during treatment for delirium are at greater risk for development of NMS [1].

Studies in the psychiatric population have shown that psychomotor agitation [18], higher doses of neuroleptics over short periods [17], and intramuscular injection of drugs [19] are more likely to be observed in patients with NMS. Other authors suggest that such factors as organic brain disease, sympathoadrenal hyperactivity and infections are NMS predisposing factors [10] (Tab. 2).

Differential diagnosis. Differential diagnosis in suspicion of NMS is of the utmost importance since NMS is a diagnosis of exclusion. Among conditions which should be differentiated with NMS, a few are life-threatening: acute lethal catatonia and heat stroke. The list of disorders which may be mistaken for NMS is extensive and presented in Table 3.



Table 2. NMS risk factors [1, 2, 5, 6, 11]

Previous NMS
Previous ECT
Known cerebral compromise/concurrent organic brain disease/brain trauma
Psychomotor agitation
Prolonged need for restraint or seclusion
Catatonia
Affective disorder
Mental retardation
Dehydration
Malnutrition
Postpartum
Parkinson's disease
Alcoholism
Young and male
Japanese nationality
High serum creatine phosphokinase
High potency antipsychotics
IM therapy (e.g. haloperidol, fluphenazine)
High doses of antipsychotics over short periods
Abrupt or recent changes of antipsychotic therapy
Rapid neurleptisation
Concurrent MAOI's
Polypharmacotherapy (antipsychotics + carbamazepine or lithium)

Iron depletion NMS – neuroleptic malignant syndrome, ECT – *Electroconvulsive therapy*, IM – intramuscular, MAOI – *Monoamine oxidase inhibitors*

Acute lethal catatonia (ALC) is a very rare psychiatric disorder. Some of its features (muscle rigidity, hyperthermia and akinesia) are also observed in NMS patients. Severe akinesia results from long-term treatment with neuroleptics which may lead to extensive loss of dopamine [5]. In differentiating between NMS and ALC, a detailed history during the three weeks prior to the onset of symptoms takes highest priority since all additional tests (CT scan EEG and laboratory findings) have proved to be of no value. While taking the history, features such as anxiety or agitation, neglect of previous interests, depression and emotional withdrawal should be sought by physician. The diagnosis of ALC is more likely if the above symptoms are accompanied by circling movements of the arms, torsion spasms, grimacing, posturing, waxy flexibility, echolalia, echopraxia and mutism [1,11,20]. Death in course of ALC may result from cardiovascular compromise or respiratory arrest.

One of the conditions with which NMS should be differentiated is heat stroke. Due to their anticholinergic (blockage of heat dissipation and sweating) and antidopaminergic (influence on thermoregulation) effect, neuroleptics predispose to hyperthermia. Heat stroke may develop when such factors as agitation or excessive exercise, hot and humid weather with limitation of fluid intake, exist. Abrupt onset, often accompanied by seizure, absence of sweating and extrapyramidal signs and evidence of excessive physical exercise or exposure to high temperature, are features which help differentiate between heat stroke and NMS [1, 2, 5, 6]. Heat stroke requires extensive cooling (placing icepacks over areas where there are large superficial blood vessels – axillae, groin, neck), rehydration, fanning the completely

Table 3. NMS differential diagnosis [1, 2, 5, 6, 11, 21]

Anesthetic – induced malignant hyperthermia
Acute lethal catatonia
Heat stroke
Central nervous system infections
Drug interactions with MAOI's
Central anticholinergic syndrome
Toxic encephalopathy
Serotonin syndrome
Pheochromocytoma
Thyreotoxicosis Lithium toxicity
CNS tumor
Nonconvulsive status epilepticus
Sepsis
Salicylate poisoning
Benign extrapyramidal side effects
Agitated delirium
Substances of abuse (hallucinogens, amphetamines)

Withdrawal from alcohol, baclofen, dopamine agonists NMS – neuroleptic malignant syndrome, MAOI – *Monoamine oxidase inhibitors*, CNS – *central nervous system*

undressed patient, on whom tepid water is sprayed, while simultaneously monitoring core body temperature [4].

In patients on neuroleptics who develop signs and symptoms of NMS, all psychotropic medications should be discontinued until their etiology is revealed. While making a diagnosis, the physician should perform a careful physical examination, obtain a detailed history, and run the following diagnostic tests: creatine phosphokinase concentration, white blood cell count, liver enzymes tests, TSH, toxicology screening, catecholamines levels, renal function (creatinine, BUN and urine analysis), EEG, head CT scan, lithium concentration, and lumbar puncture [1, 7].

Treatment. The success in NMS treatment depends on prompt diagnosis and discontinuation of neuroleptics. Supportive therapy is the first-line management in NMS treatment [4], with proper nutrition, hydration (intravenous fluid resuscitation should be aggressive) and reduction of fever being among the most important actions. Hemodialysis is not used since it does not remove neuroleptics from the blood stream. Possible complications, such renal failure, acidosis and hypoxia, should be treated promptly. It is critical to monitor and correct any electrolyte abnormalities. Studies results suggest that bicarbonate loading may prevent renal failure [15]. In immobilized patients, a low-dose of low-molecular-weight heparin (LMWH) should be used to prevent venous thrombosis.

There are doubts regarding any additional therapies since, in most cases, NMS is a self-limiting disorder, and supportive therapy and neuroleptic discontinuation should be enough to reverse the symptoms [4]. The evidence on specific pharmacological treatments in NMS is limited; however, clinical reports support empirical and often off-label management approaches [22].

In milder cases of NMS, orally or parenterally administered benzodiazepines may ameliorate symptoms, even though they do not have a protective effect; 1–2 mg of lorazepam given every 4–6h appears to be an effective and safe management



in patients with milder cases of NMS and in whom catatonic symptoms dominate [4].

Rosenberg and Green [23], after extensive review of the literature, state that bromocriptine (2.5–5mg p.o. or by nasogastric tube every 8h) was effective after one day of treatment on NMS. The drug is relatively well tolerated and rigidity decreases after the first few hours. This effect is followed by a decrease in temperature. Blood pressure also usually normalizes within a few hours; however, hypotension seems to be a side-effect which limits the usage of bromocriptine, and it should be used with caution in patients at risk of aspiration since it may precipitate vomiting [1, 4].

In cases of malignant hyperthermia, dantrolene is the first line-treatment. This drug (1–2.5mg/kg body weight i.v. every 6h for 48h) should be used only in severe cases of NMS (rigidity, hypermetabolism and extremely high temperature). The symptoms may reoccur if dantrolene is discontinued prematurely. Dantrolene acts by blocking calcium release from sarcoplasmic which decreases calcium in muscle contracture. This leads to muscle relaxation accompanied by decrease in temperature. Hepatic toxicity and respiration impairment are the most limiting side-effects. Dantrolene can be safely combined with bromocriptine, amantadine or benzodiazepines; however, administered with calcium channel blockers it may lead to cardiovascular collapse [1, 4, 24].

In some cases of NMS, another dopaminergic drug, amantadine, has been used successfully. Amantadine used alone (200–400mg/day p.o. or by nasogastric tube every 8h), or combined with other medications, reduces the time to recovery and mortality rate in NMS [1, 4].

In moderate and severe NMS, pharmacotherapy is the first-line treatment. Electroconvulsive therapy (ECT 6–10 bilateral treatment) should be considered as second-line treatment. ECT is proven to have a positive effect on fever, sweating and level of consciousness [25, 26, 27]. ECT was effective even after pharmacotherapy had failed. Response was observed after the first several treatments and not affected by such factors as age, gender, features of NMS or psychiatric disorder. ECT is relatively safe in NMS; however, extra care should be taken while using succinylcholine in patients with rhabdomyolysis to avoid cardiovascular complications or hyperkalemia [4, 25].

There are also other methods which have been used in NMS management: werapamil, carbidopa, L-dopa, plasmapheresis or pancuronium [5], although their efficacy has not been proved. NMS treatment usually last 5–10 days, provided neuroleptics depot formulations were not used [5].

Reintroduction of neuroleptic agents. Reintroduction of antipsychotic treatment after NMS involves a risk of redeveloping of NMS, which is as high as 30% [28, 29, 30]. However, by taking proper precautions, patients who require antipsychotics may be treated safely. The precautions involve, but are not limited to: consideration of alternative treatment (e.g. ECT, lithium carbonate), reduction of risk factors (e.g. proper hydration and nutrition in neuroleptic-treated patients, low-potency neuroleptics), obtaining and analyzing detailed history of previous episodes, and monitoring of early signs of NMS. The physician should wait approximately two weeks after recovery from NMS before introducing neuroleptics again in the patients [4, 31]. Furthermore, a written informed consent should be

obtained from patients and family members regarding the risks and benefits of restarting antipsychotic treatment. To summarise, the safest approach is gradual titration of low-potency conventional neuroleptics or atypical antipsychotics, especially clozapine.

CONCLUSIONS

NMS is a rare but potentially fatal complication of antipsychotic treatment with an incidence estimated at 0.01–0.02%. The introduction of atypical neuroleptics and higher awareness of NMS has resulted in a decrease of NMS incidence. There are three symptoms which are considered as major and indicate a high probability of NMS: muscle rigidity, hyperthermia and elevated creatine phosphokinase concentration. NMS is a diagnosis of exclusion and clinicians must be vigilant in detecting the early signs of NMS. Prevention through more conservative use of antipsychotics, reduction of risk factors, early diagnosis and proper management are of utmost importance in suspicion of NMS. First line management is discontinuation of neuroleptics and proper supportive care (cooling, hydration, patients monitoring). In more severe cases, the introduction of benzodiazepines, aopaminergic drugs (bromocriptine and amantadine) or dantrolene may be indicated. If a patient requires antipsychotic treatment two weeks after resolution of NMS, low doses of low-potency typical neuroleptics or atypical neuroleptics should be initiated, and the patient monitored carefully.

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