NEUROLEPTIC MALIGNANT SYNDROME FOR THE EMERGENCY NEUROLOGIST

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ABSTRACT

The neuroleptic malignant syndrome (NMS) represents an infrequent but serious complication of the treatment with neuroleptics, mainly typical but also atypical. NMS can occur at any age and irrespective of gender and comorbidities, while the risk factors are incompletely known. NMS manifestations are marked but non-specific, making possible the presentation of such patients to the emergency department (ED) of any speciality, neurological in particular. The poor prognosis of NMS derives from its difficult diagnosis and its severity, leading to serious complications and even fatalities when adequate treatment is not applied as early as possible. The purpose of this article is to help assist in accurate assessment management of a patient presenting with signs and symptoms of neuroleptic malignant syndrome (NMS) in the emergency department (ED).

Keywords: neuroleptic malignant syndrome, emergency, neurologic.

INTRODUCTION

NMS was first described by Delay and colleagues in the 1960s. It is believed to occur as a rare, but life-threatening, adverse drug reaction triggered by neuroleptic antipsychotic medications or other medications. The clinical presentation consists of fever, extrapyramidal signs and symptoms, altered mental status and dysautonomia.

EPIDEMIOLOGY

The currently accepted frequency is lower than initially reported and parallels the rate of antipsychotic medication use and the awareness regarding NMS. The reported incidence varies from 3% of patients treated with neuroleptics (1) to 0,07-0,2% from the general population (2). The widespread use of antipsychotic medication needs also to be counterbalanced by an increased awareness in order to better diagnose and manage NMS.

NMS development predominates in young adult males, with a men to women ratio of 2:1 (2,3), irrespective of age, including children and both genders (unu'), the incidence peaking towards 40 years of age when the probability of receiving neuroleptic treatment is highest (3,4).

ETIOLOGY AND PATHOGENY

NMS is considered the most severe neurological acute side effect related to the use of neuroleptic medications, initially reported in association with the use of the older generation neuroleptics (eg, haloperidol, fluphenazine) but now recognized to occur in association with every commercially available antipsychotic (2,3).

Although the exact pathophysiologic mechanisms of NMS have not yet been clarified, it is generally believed to result from an altered central dopamine-related transmission, mostly as a consequence of dopaminergic blockade (2) or of decreased dopamine availability. Dopamine is a neurotransmitter with

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impact on central structures like the striatum and hypothalamus, the dopamine blockade explaining the occurence of muscular rigidity and pyrexia, altered thermoregulation and reduction of heat dissipation. Decreased action of dopamine in the mesocortex, basal ganglia and spinal cord can account for the alterations of mental status (emotions, thoughts, concentration), autonomic regulation and biological rhythms seen in NMS. (2,4).

Dopamine also displays peripheral effects that impact on the muscle contraction (suppressed) and relaxation process, the dopaminergic blockade leading to an increase of calcium release from the sarcoplasmic reticulum (5) contributing to the increased contractility and hyperthermia, possibly in the presence of anomalies of the muscle membrane (5,6).

Other physiopathological hypotheses formulated with regard to NMS include sympatoadrenal hyperactivity (2,7), GABA hypoactivity ($GABA_A$ receptors), increased serotoninergic activity at the 5-HT_{1A} receptors and decreased at the 5-HT_{2A} receptors (8,9) and glutamatergic hypoactivity at the NMDA receptors (10).

The list of risk factors for the development of NMS is still under debate but treatment with a high-potency neuroleptic is the most important one. Even if associated with a lower degree of dopaminergic blockade, possibly accounting for a lower incidence of NMS and of extrapyramidal side effects, atypical neuroleptics like e.g. clozapine, quetiapine, olanzapine, aripiprazole, risperidone, perospirone, zuclopenthixol have been demonstrated not to be devoid of this side effect (11,12,13,14,15,16,17,18, 19). 96% of all cases manifest in the first 30 days of treatment (1), the risk persisting even within 22 days after withdrawal of the causing drug (2). Other drugs associated with the development of NMS include metoclopramide, amoxapine, lithium, anticholinergics and some antidepressants, exposure to cocaine, as well as an association with a dopamine agonists withdrawal. Until now, no clear relationship was demonstrated between NMS and the serum level of the offending drug (4), a recent increase in dosage, the individual dose, the duration of exposure and the type of neuroleptic (long-acting versus short-acting) (1,4). A genetic predisposition was also observed (2) in homozygots for mutations of the citochrome P4502D.

Further risk factors are male gender, stress and dehydration (5), without a clear relationship with high environmental temperature and humidity (20), possible concomitant conditions including hyponatremia, cerebral trauma and organic disorders (4) and/or debilitated state, malnutrition and alcoholism (1).

Typical neuroleptics	Atypical neuroleptics
Low potency:	- Amisulpride
- Chlorpromazine	- Aripiprazole
- Levomepromazine	- Asenapine
- Mesoridazine	- Blonanserin
- Thioridazine	- Clotiapine
Medium potency:	- Clozapine
- Loxapine	- Iloperidone
- Molindone	- Mosapramine
- Perphenazine	- Olanzapine
- Thiothixene	- Paliperidone
- Trifluoperazine	- Perospirone
High potency:	- Quepin
- Droperidol	- Quetiapine
- Fluphenazine	- Remoxipride
- Haloperidol	- Risperidone
- Prochlorperazine	- Sertindole
- Zuclopenthixol	- Sulpiride
	- Ziprasidone
	- Zotepine

***Table 1**. Typical and atypical neuroleptics.*

CLINICAL FEATURES

NMS is a very heterogeneous condition with varying degrees of severity and insidious or fulminant onset (10) of hyperthermia and extrapyramidal manifestations, changes in the level of consciousness and dysautonomia. NMS with atypical presentations have also been reported to be taken into account. Muscular rigidity and hyperthermia, major diagnostic features of NMS, may be absent at onset or during the entire duration (2,3).

A thorough neurological examination should be performed in all patients suspected with NMS. Ex-

Physical findings	Laboratory findings
- tachycardia (> 100 beats/ min.), even arrhythmias - abnormal blood pressure, frequently hypertension or BP variability - tachypnea (≥ 25 breaths/ min.) - diaphoresis - sialorrhea - lead-pipe muscle rigidity - trismus - Babinski sign - opisthotonus - chorea - altered mental status - mutism - other: palor, rash, dyspnea	- increased CK levels - myoglobinuria - leukocytosis - increased transaminases

***Table 2**. Clinical and laboratory findings in NMS.*

trapyramidal manifestations predominate amongst the clinical features of NMS. The increased, lead-pipe rigidity affects mainly the trunk and can account for the observed tachypnea but may also manifest as trismus and opisthotonus. The examiner can also demonstrate a shuffling gate, akinesia, bradykinesia, dyskinesia, rest tremor, chorea, acute dystonia or oculogyric crisis. The physical examination can demonstrate a positive cogwheel and Babinski's sign.

Psychomotor agitation may be present at onset or develop later, together with other neuropsychiatric manifestations including mutism, confusion, delusion, hallucination, catatonia, stupor or coma.

The mortality rate associated with NMS varies greatly in the literature, from 0,01-0,2% to 14-30% (1), significantly higher in the presence of serious complications like acute renal failure (50%) (2).

Rhabdomyolysis
Acute renal failure
Acute respiratory failure
Myocardial infarction
Brain lesions
Seizures
Hepatic failure
Disseminated intravascular coagulation
Escherichia coli fasciitis
Sepsis

Table 3*. Frequent complications of NMS.*

DIAGNOSIS

The diagnosis of NMS is based on medical history, clinical and laboratory findings together with a detailed differential diagnosis.

The essential features of NMS are the development of severe muscle rigidity and pyrexia (usually above 38°C) in an individual with a history of neuroleptic treatment (in the last 1 to 4 weeks for oral agents, 2 to 4 weeks for long-acting, depot agents) and in the absence of another known cause. In addition, more than 5 of the following symptoms must be present: diaphoresis and sialorrhea, tremor, incontinence, changes in the level of consciousness ranging from confusion to coma, tachycardia, elevated or labile blood pressure, tachypnea or hypoxia, leukocytosis and metabolic acidosis, and laboratory evidence of muscle injury (e.g., elevated creatine phosphokinase or myoglobinuria) (2,3,4).

Findings obtained from electromyography, electroencephalography, cerebral computed tomography and muscular biopsy are not essential for the positive diagnosis of NMS (4).

DIFFERENTIAL DIAGNOSIS

A detailed differential diagnosis, including a careful neurological and psychiatric examination, can increase the diagnostic yield due to the heterogeneity and lack of specificity of NMS presentation but can only be achieved through multidisciplinarity.

NMS needs to be differentiated from many neuromuscular conditions, including: Parkinson's disease, meningitis, encephalitis (especially acute viral), multiple system atrophy (Shy-Drager syndrome), epilepsy and status epilepticus, stroke, space-occupying lesions, including CNS neoplasm, cerebral vasculitis, malignant hyperthermia or severe dystonia.

A detailed discussion of the differential diagnosis in NMS is beyond the scope of this article. Other possible differential diagnosis can be found in table 4.

Psychiatric	**Toxic exposures**
Delirium Depression / mania with catatonic features Catatonic schizophrenia / psychosis Lethal catatonia	Heat stroke Amphetamines Anticholinergic agents Cocaine Excess serotonin (serotonin syndrome) Extrapyramidal drug reactions Monoamine oxidase inhibitors Salicylates (Aspirin overdose) Heavy metal poisoning (e.g. lead, arsenic) Side-effects associated with atypical antipsychotics Rapid withdrawal of dopaminergic medications (e.g., L-dopa) Dopamine depleting medications (e.g., Reserpine, Tetrabenazine) Lithium toxicity Allergic drug reactions Phencyclidine intoxication Alcohol / sedative (benzodiazepine, barbiturate) withdrawal Strychnine poisoning
Metabolic Hyperthyroidism (thyrotoxicosis) Hypocalcemia Hypomagnesemia Pheochromocytoma	
Infectious Rabies Sepsis Tetanus Botulism	
Miscellaneous Acute intermittent porphyria Systemic lupus erythematosus	

Table 4*. Other differential diagnosis of NMS.*

TREATMENT

NMS may present as a neurological emergency, hence the need for early diagnosis, withdrawal of the offending drug, supportive and pharmacologic measures under close monitoring.

Supporting measures include temperature reduction, adequate hydration (especially in the presence of rhabdomyolysis)(5), maintaining the hydroelectrolytic balance which sometimes may

require dialysis, venous thromboembolism prophylaxis and cardiorespiratory and hemodynamic support.

The pharmacologic treatment of NMS is also challenging due to lack of double-blind or placebo-controlled clinical trials, to the heterogeneity of the disease, the presence of complications which can significantly change the approach to management. Furthermore, the oral route of administration can prove difficult in the acute stages and the effective doses may greatly vary interindividually. Combining different drugs has failed to demonstrate improved efficacy and cannot be routinely recommended.

The dopaminergic drugs play an essential role in the treatment of NMS. Apomorphine administered subcutaneously is considered first-line therapy, useful even as monotherapy (16). Bromocriptine acts by the activation of the postsynaptic dopaminergic D2 receptors, thus contributing to the reversal of the hypodopaminergic state of NMS and to the improvement of an altered mental status and of rigidity.

The levodopa-based treatment may be administered in combination with carbidopa or benserazide and can be effective as a first-line treatment in NMS, irrespective of the severity of presentation, by addressing most of the NMS features.

Benzodiazepines may improve symptoms (rigidity, mental status and psychomotor agitation) and speed of recovery, particularly in milder cases (20), supposedly potentiating the GABAergic activity and indirectly increasing the dopaminergic activity at the level of basal ganglia and substantia nigra (21).

Amantadine, an antagonist of the NMDA receptor that increases the dopamine release from intact dopaminergic terminals, mainly reduces hyperthermia.

Dantrolene sodium is a peripheral myorelaxant used to correct the increased muscle tone and hyperthermia. It closes the ryanodine receptors within the sarcoplasmic reticulum, thereby decreasing the calcium release (4). In the acute phase it should be administered intravenously, then orally. It's value has been challenged with regard to its real therapeutic value and safety (2,22). Other intravenous myorelaxants been used in the treatment of NMS include pancuronium, rocuronium and mivacurium.

Electroconvulsive therapy is thought to increase the release of dopamine and could prove effective in cases where most other measures have failed, especially with regard to hyperthermia, diaphoresis, mental status, consciousness and the underlying psychiatric pathology but should not be used in clinically unstable patients (23).

Glucocorticoids can also prove useful in the treatment of NMS due to their dopaminergic and lysosome membrane stabilization effect (24) based on the presence of active glucocorticoid receptors within the ventral tegmental area and substantia nigra.

Secondary prophylaxis is aimed to inform these patients about their increased risk of NMS recurrence and to apply measures in order to avoid neuroleptics or to avoid recurrence in cases where re-exposure to neuroleptics is deemed necessary.

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