
THE NEUROLEPTIC MALIGNANT AND SEROTONIN SYNDROMES

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THE NEUROLEPTIC MALIGNANT SYNDROME

The advent of neuroleptic medications in the 1950s led to a revolution in the care of patients suffering from psychiatric illnesses. Like all pharmacotherapeutic agents, however, neuroleptic agents soon would be found to have unwanted side effects. Among these is an adverse reaction that can be particularly devastating, termed the *neuroleptic malignant syndrome* (NMS). First described in the French medical literature in the 1960s,¹⁰ the incidence of NMS is estimated at approximately 1.0% of patients treated with neuroleptics. The syndrome most commonly occurs within the first 3 to 9 days of therapy but can occur after a patient has been taking neuroleptics for a long time. NMS is thought to be an idiosyncratic drug reaction that is not dose related. It has been reported to occur after a single dose of a neuroleptic agent. A person who has developed NMS during treatment with a specific neuroleptic agent can actually be treated with the same agent at a later time without redeveloping the syndrome,^{40, 53} although recurrences have been reported.

NMS is most closely associated with the use of the high-potency neuroleptics, such as haloperidol and thiothixene. It is believed to occur less frequently with the low-potency neuroleptics such as chlorpromazine and mesoridizine, although this finding is controversial. In addition, the newer "atypical" neuroleptics, such as clozapine, risperidone, and olanzapine, which have been marketed as having fewer side effects than do the older neuroleptic agents, also have been associated with the NMS.^{3, 13} The syndrome has been reported in the setting of treatment with L-dopa agents, as in patients with parkinsonism.²⁴

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Pathophysiology

The etiology of NMS is related to a dysregulation of the dopaminergic system.²⁰ In the treatment with antipsychotic neuroleptic agents, there is an iatrogenic blockade of dopaminergic transmission, particularly involving the D₂-receptor system; in the use of L-dopa in parkinsonism there is an iatrogenic enhancement of dopaminergic transmission. In both contexts, the pathophysiology of NMS is believed to be due to dopaminergic blockade in the basal ganglia and in the hypothalamus.²² Although this seems at first to be counterintuitive in treatment of parkinsonism, NMS usually occurs with sudden decreases in the dosage of L-dopa, amounting to a relative deficiency state compared with when the patient was being treated with a higher dose of L-dopa. It has also been postulated that the glutamatergic system of neurotransmission could be involved in NMS, thus explaining the proposed benefit of amantadine, a NMDA S-type glutamate receptor antagonist, in the treatment of NMS.^{3,24}

Contributing factors to developing NMS include ambient heat and dehydration; underlying brain damage and dementia (which may have already damaged dopaminergic pathways); and high dosing of neuroleptics, although this would appear to contradict our understanding of NMS as an idiosyncratic drug reaction (the apparent contradiction could be resolved conceptually by hypothesizing that there is a genetic dose-dependent vulnerability).

Clinical Features

The constellation of signs and symptoms that comprises the NMS is essentially a triad of hyperthermia (autonomic instability), encephalopathy, and skeletal muscle rigidity. In addition to rigidity, the patient can have akinesia or dystonia. Autonomic instability is an important feature of the syndrome, and, in addition to causing hyperthermia, it can result in blood pressure instability, diaphoresis, and tachycardia. Clinical features are accompanied by the laboratory findings of increased creatine kinase (CK), leukocytosis, and myoglobinuria.⁵ CK elevations of up to 60,000 IU/L have been reported. White blood cell counts are typically in the range of 10,000 to 40,000 cells/mm³ and can be accompanied by a shift to the left.³⁶ One must remain alert to the fact that patients with NMS can develop concurrent infections that could complicate management and result in a refractory response to treatment. Suspicion of a comorbid process is aroused if a patient continues to be hyperthermic despite decreasing CK levels or if symptoms persist past 2 weeks, the average time course of NMS.³⁶

One of the factors that can delay arriving at the correct diagnosis is the occurrence of a *forme fruste* of the syndrome, in which some or all of the classic clinical features are initially absent. Severe NMS, for example, has been reported to present without hyperthermia or without muscular rigidity.^{29, 50} Clearly, this attenuated form of the syndrome poses a diagnostic dilemma, which can be complicated further by its unpredictable time of onset in relation to initiation or withdrawal of therapy.⁴⁵

The mortality rate in NMS is estimated at 12% to 20%. The most significant cause of morbidity and mortality is renal failure secondary to the large amounts of myoglobin produced by rhabdomyolysis,⁵ followed by respiratory failure owing to aspiration pneumonia.⁴⁸ Aspiration in the setting of NMS can occur secondary to obtundation as well as to dysphagia. Other causes of mortality and morbidity include sudden cardiac death from myocardial infarction, acute cardiac failure, or a fatal dysrhythmia. Thrombocytopenia and disseminated intra-

vascular coagulation (DIC) have been reported.^{12, 24} It is essential to monitor the electrolyte status of patients with NMS closely because hyperkalemia, hyponatremia, and hyponatremia can occur.²⁹

Differential Diagnosis

One of the many challenges involved in the treatment of NMS involves making the correct diagnosis. Errors can occur in either direction, that is, the tendency to overdiagnose as well as the tendency to underdiagnose the syndrome. In the case of the overdiagnosis, the principal danger lies in missing an infectious process (e.g., meningoenzephalitis). The underdiagnosis can involve underestimating the associated autonomic instability associated with the syndrome, or ignoring the potential complications of rhabdomyolysis. In the case of either the overdiagnosis or underdiagnosis of NMS, the opportunity for the most appropriate treatments to be initiated in a timely fashion is missed.

The differential diagnosis of patients with NMS includes all entities that can present with any combination of encephalopathy, fever, and rigidity. This includes central nervous system (CNS) infections, the serotonin syndrome (defined later in this article) heat stroke, acute dystonic reactions, and drug toxicities (e.g., monoamine oxidase inhibitor, cholinergic, or lithium toxicities). The differential diagnosis of NMS also includes vasculitis. In the setting of a primary CNS vasculitis, the usual vasculitis work-up can be normal, and, in select cases, brain biopsy is necessary to confirm the diagnosis. Malignant hyperthermia is another diagnostic entity that should be considered when there is a history of anesthesia.

Lethal catatonia,^{2, 30} part of the group of entities known as *malignant catatonia*,⁴³ deserves special mention in the differential diagnosis of NMS. Like NMS, lethal catatonia and malignant catatonia can present as an encephalopathy accompanied by fever.^{37, 40} Some authors have claimed that it is not possible to distinguish between NMS and lethal catatonia, whereas others have suggested that catatonia in general could be a prodrome of NMS. The importance of distinguishing the catatonias from NMS lies in the treatment; it is crucial to add a benzodiazepine to the pharmacotherapeutic regimen of any patient suspected of catatonia.^{15, 39, 52}

Diagnostic Testing

NMS poses a tremendous challenge to the clinician. A careful work-up is indicated, which includes the following: serum electrolyte levels, creatinine and blood urea nitrogen levels, complete blood count (including platelet, coagulation studies, liver, and thyroid functions), serum CK, urine myoglobin, and blood and urine cultures. A chest radiograph and electrocardiogram are also indicated. An arterial blood gas determination should be considered when pulmonary complications are suspected and to help to determine whether pulmonary embolism is present.

An emergent, noncontrast head CT is necessary to assess for intracranial processes. An electroencephalogram (EEG) can be valuable to assess for nonconvulsive status epilepticus or viral encephalitis. A lumbar puncture is a routine part of the work-up of any patient for whom the diagnosis of NMS is being considered.³⁸

The patient with NMS must be carefully monitored throughout the course of the syndrome for possible complications, including, but not limited to, renal

failure, electrolyte abnormalities, dysrhythmia, aspiration pneumonia, sepsis, and pulmonary embolism secondary to the formation of deep vein thromboses (DVT). In the patient not making a reasonably rapid recovery, it is appropriate to repeat a full diagnostic work-up, including a repeat lumbar puncture.

Management

Management of NMS focuses on withdrawal of the neuroleptic medication and meticulous supportive care, which includes aggressive hydration. Because renal failure is the commonest complication in NMS, strategies must be directed at managing the elevations of CK, with its resulting myoglobin load to the kidneys. Fluid input and output must be monitored carefully, and a urinary output of at least 50 to 100 mL/hr maintained. Autonomic instability results in increased "insensible losses," with up to an additional 500 mL lost for each degree Celsius rise in body temperature.⁵⁵ The use of cooling blankets is essential to decrease body temperature; antipyretic agents can be helpful if an infection is a comorbid factor. Vital signs must be monitored carefully, and a nasogastric tube is indicated given the danger of aspiration. DVT prophylaxis should be started as soon as possible. Patients with NMS should be admitted to an intensive care setting.

In addition to aggressive supportive measures, several specific treatments are mentioned in the literature. Dantrolene sodium, 3 to 5 mg/kg IV divided t.i.d. or q.i.d., has been recommended to treat skeletal muscular rigidity.^{9, 51} Dantrolene sodium exerts its therapeutic effect by means of the blockade of calcium release from the muscle fiber's sarcoplasmic reticulum. Bromocriptine, 5 mg q.i.d. by nasogastric tube, has also been recommended.¹¹ This can be increased to a maximum of 40 mg/d. The therapeutic effect of bromocriptine is related to its dopamine agonism, resulting in enhancement of dopaminergic transmission. Some authors have recommended the addition of carbidopa/levodopa, 25/100 by nasogastric tube or intravenous L-dopa.^{21, 34} Other proposed treatments of NMS include pancuronium,^{18, 42} carbamazepine,⁴⁹ amantadine,¹ anesthesia,¹⁸ and plasmapheresis.¹⁶

An additional mode of treatment that has been used successfully for NMS is electroconvulsive therapy (ECT).^{23, 27, 31} Its mechanism of action is not completely elucidated, but reports of its efficacy are encouraging, especially because it is also efficacious in the treatment of most types of catatonia.²³ In preparation for ECT, patients are paralyzed; in NMS, in which there is substantial muscle breakdown, a depolarizing agent is contraindicated owing to its tendency to increase serum potassium levels.¹⁷ Instead, patients with NMS who receive ECT are paralyzed with a nondepolarizing agent.

Although the various specific treatments presented raise interesting questions regarding various aspects of the pathophysiology of NMS, these treatment approaches have not been studied using well-designed methodologies. In fact, most of the proposed therapies are supported by single case reports only. An important study by Rosebush et al raises serious questions not only about the efficacy of these treatment measures but also about the suggestion that in some cases, the various specific therapies actually can result in a prolongation of the syndrome.⁴¹ As a result, presently it is not possible to make clear treatment recommendations; management of NMS centers primarily on supportive care, with the role of specific treatment modalities remaining uncertain.

THE SEROTONIN SYNDROME

The advent of antidepressant pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) was greeted with enthusiasm owing to their low side-effect profile and high degree of therapeutic efficacy. This class of drugs, however, which enhance serotonergic neurotransmission with only a relative increase in the actual level of serotonin, can result in a toxic state that resembles NMS. Of note, NMS occurs as an idiosyncratic drug reaction, whereas the serotonin syndrome is a toxic effect that is thought to be due to a hyperstimulation of 5-HT_{1A} receptors in the brain and spinal cord.⁴⁶

The *serotonin syndrome* is characterized by mental status changes and a variety of autonomic and neuromuscular manifestations. In most cases, two or more medications known to increase the activity of serotonin are implicated. It was first described in association with the administration of monoamine oxidase inhibitors.³⁵ More recent literature has implicated the tricyclic antidepressants (TCAs) and the SSRIs. Increased serotonin activity can result from inhibition of serotonin metabolism, potentiation of serotonin activity, activation of serotonin receptors, inhibition of serotonin uptake, or increased substrate supply. Generally, two or more agents possessing at least one of these characteristics must be coadministered for the syndrome to develop, although cases involving single agents have been reported.^{28, 32} In most cases, symptoms develop soon after the addition of a new agent or a change in the dose of one already being taken.³²

Monoamine oxidase inhibitors (MAOIs) increase serotonin levels by inhibiting the breakdown of serotonin. Many of the MAOIs cause irreversible enzyme inhibition. Consequently, the serotonin syndrome can result from initiating new therapies that increase serotonin weeks after an MAOI has been discontinued.⁴⁶ Newer MAOIs have tried to obviate this problem by targeting specific subtypes of the enzyme, although toxicities have still been reported when they combined with SSRIs.^{26, 47} SSRIs are well absorbed, metabolized in the liver, and reach peak levels within several hours. Doses should be decreased in patients with liver disease to prevent inadvertent toxicity. Fluoxetine has the longest half-life (2-3 days). As with the MAOIs, a sufficient drug-free interval must exist between the time an SSRI (particularly fluoxetine) is discontinued, and use of another drug having activity at central 5-HT_{1A} receptors is begun.

Clinical Features

The serotonin syndrome consists of a cluster of findings that include encephalopathy, hyperreflexia, nausea and vomiting, and marked autonomic instability.⁴⁴ It can be confused with NMS and other encephalopathic states, thus emphasizing the importance of obtaining a comprehensive medication history. Altered mental status is observed in approximately 40% of patients.^{22, 46} Patients frequently present as agitated, restless, or even hypomanic. Less often, they are drowsy or in coma. Neuromuscular symptoms are seen in 50% of patients and include myoclonus, rigidity, and tremor.³² Hyperreflexia is consistently found, and along with rigidity, is frequently more pronounced in the lower extremities. Diaphoresis and mild elevations in temperature are seen in about 50% of cases. Rhabdomyolysis, hyperkalemia, renal failure, DIC, and seizures are all rare but reported findings. The serotonin syndrome is usually self-limited, with an uneventful resolution once the inciting agent has been discontinued.

Despite the similarities between NMS and the serotonin syndrome, there are clinical features that can be helpful in distinguishing the two. NMS is

more likely to present with extrapyramidal signs, very high fevers, dysphagia, incontinence, and sialorrhea. Conversely, patients with the serotonin syndrome are more likely to present with myoclonus, hyperreflexia, and ataxia. Because the serotonin syndrome is basically a hyperserotonergic state, it can be compared to a naturally occurring pathologic hyperserotonergic state (i.e., the carcinoid tumor), thus explaining the occurrence of diarrhea, diaphoresis, and vomiting in these patients. It cannot be overemphasized, however, that frequently one sees partial forms of these syndromes, in which, for example, only a mild encephalopathy can be present, perhaps accompanied by mild autonomic instability. In such cases, the distinction between the syndromes can be very hard to discern. Likewise, because patients with the serotonin syndrome initially can present with complaints of anxiety or mental status alteration, it should be considered carefully, especially in patients who have recently had a change in their pharmacologic management.

Management

The treatment of the serotonin syndrome begins with the immediate withdrawal of the offending drug. Analogous to the treatment of NMS, the institution of aggressive supportive measures, including intravenous hydration, is essential. Careful monitoring of the patient's autonomic parameters and seizure precautions are indicated. Muscle contractions should be limited, because if unchecked they can lead to fever, rhabdomyolysis, and respiratory compromise.^{6,32} Benzodiazepines are recommended (particularly clonazepam) because they are effective in controlling myoclonus.³³

Syndrome specific treatments have been proposed, including the use of serotonin antagonists (e.g., cyproheptadine and methysergide); however, no well-designed studies have been performed.³² Treatment with propranolol has been recommended based on the theoretical basis that this is a 5HT-receptor antagonist,³⁴ although one case report of a fatality in a patient on propranolol has made some clinicians skeptical of this treatment.²⁵ Other interventions of undetermined benefit include chlorpromazine⁴ (which must be avoided, along with metaclopramide and other phenothiazine derivatives, in patients with suspected NMS), and benadryl.⁷ Presently, treatment of the serotonin syndrome is based primarily on removing the offending agent, meticulous supportive care, and judicious use of benzodiazepines. Recommendations for other treatments await further study.

CONCLUSION

An intensive review of the literature on the NMS and the serotonin syndrome reveals that these two syndromes have many similarities between each other and with other entities, such as malignant catatonia. There are many overlapping aspects of the clinical presentation, which is complicated further by the *forme fruste* of either syndrome. Indeed, the overlapping components of these syndromes with each other and with the various types of catatonia have led some to propose that they are all within the same spectrum of a single disorder.¹⁴

It might not necessarily be critical, nor even possible, to determine precisely with which of these entities one is dealing. Rather, it is essential to remove the precipitating drugs immediately, and to institute supportive measures, including

hydration, cooling, and intensive physiologic monitoring. Maintaining a broad-based differential diagnosis throughout the diagnostic evaluation is critical ultimately to making the correct diagnosis. Syndrome-specific interventions are of questionable value and should be used with caution pending the results of further investigation. Indeed, it has been proposed that initiating syndrome-specific interventions could even make recovery slower than if aggressive supportive measures were used exclusively.¹⁹

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