Diagnostic uncertainty in a case of neuroleptic malignant syndrome

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening condition that has been associated with antipsychotic use. Most diagnostic criteria include fever and muscle rigidity, although NMS may present without either. Diagnostic uncertainty in such cases may result in delays in diagnosis and management, leading to adverse consequences for these patients. The differential diagnosis of NMS is broad and includes a number of neurological, medical and psychiatric conditions as well as substance and medication-induced disorders. A case is described that illustrates an atypical presentation of NMS and demonstrates some of the challenges in its diagnosis. Limitations of current NMS criteria are also examined, and suggestions for future criteria are presented.

Key words: neuroleptic malignant syndrome; adverse drug reaction; antipsychotics; differential diagnosis; serotonin syndrome

RÉSUMÉ

Le syndrome malin des neuroleptiques est une affection mettant en jeu le pronostic vital qui a été associée à l'usage d'antipsychotiques. Généralement, les critères diagnostiques comprennent la fièvre et la rigidité musculaire, bien que le syndrome puisse se manifester sans ces symptômes. L'incertitude diagnostique dans de tels cas peut entraîner des délais dans le diagnostic et la prise en charge, menant à des conséquences néfastes pour ces patients. Le diagnostic différentiel du syndrome malin des neuroleptiques est vaste et comprend un grand nombre d'atteintes neurologiques, médicales et psychiatriques, ainsi que des troubles provoqués par l'usage de substances et de médicaments. Un cas de syndrome malin des neuroleptiques illustrant une présentation atypique du syndrome est décrit et démontre certains des défis liés à son diagnostic. Les limites des critères diagnostics actuels pour le syndrome malin des neuroleptiques sont aussi examinées et des suggestions pour d'autres critères sont présentées.

Introduction

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening disorder associated with the use of antipsychotics and other medications that affect dopaminergic neurotransmission. Its incidence is reported to vary between 0.02% and 3.23% of patients treated with neuroleptics.[1] While NMS has been reported primarily in association with typical antipsychotics, which have predominately dopamine (D_2) receptor antagonism activity, it has also been described with the atypical antipsychotics clozapine, risperidone, olanzapine and quetiapine, which produce

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Received: Dec. 11, 2004; final submission: Feb. 15, 2005; accepted: Apr. 12, 2005

This article has been peer reviewed.

Can J Emerg Med 2005;7(4):266-72

greater antagonism of 5-HT_2 (5-hydroxytryptamine) as compared to D_2 receptors.[2,3] We describe an unusual case of NMS associated with clozapine and risperidone, highlighting some of the diagnostic difficulties associated with this disorder. In addition, the differential diagnosis of NMS and the validity of current diagnostic criteria are discussed, with suggestions for future diagnostic criteria presented.

Case report

Mr. A, a 51-year-old man with schizophrenia and mild cognitive impairment, presented to the local emergency department (ED) with a 1-day history of confusion, general malaise, muscle aches and palpitations. Previous medical history included episodic hypotension, iron deficiency anemia and peptic ulcer disease. Medications on admission included: clozapine 250 mg po q.a.m. plus 500 mg po q.h.s, risperidone 1.5 mg po b.i.d., and clonazepam 0.5 mg po b.i.d. plus 0.25 mg po o.d. There had been no medication changes within the previous 10 months. His confusion was noted to be of abrupt onset and markedly altered from his baseline level of functioning.

He was disoriented, anxious and experiencing auditory hallucinations upon arrival in the ED. On examination his pulse was 114 beats/min, blood pressure 131/89 mm Hg, respiratory rate 16 breaths/min and temperature 36°C. Cardiovascular, respiratory and abdominal examinations were unremarkable. Neurological findings included mild rigidity with cogwheeling in the upper extremities, a resting tremor, symmetrically diminished deep tendon reflexes and a slow, shuffling gait with marked ataxia. He was incontinent of urine. A complete blood count demonstrated a leukocytosis of 13.6×10^9/L with a prominent neutrophilia and a normocytic anemia with a hemoglobin of 122 g/L. Electrolytes, BUN (blood urea nitrogen), creatinine, glucose, TSH (thyroid stimulating hormone) and liver enzymes were normal, while serum phosphate was low at 0.36 mmol/L. Serum CK (creatine kinase) was elevated at 590 IU/L with a negative MB fraction and a negative troponin. His electrocardiogram revealed a sinus tachycardia with no evidence of ischemia. The provisional diagnosis at this time was exacerbation of psychosis. Management plans included continued monitoring and serial measurement of cardiac enzymes.

The patient became increasingly agitated in the ED. He received 3 mg of lorazepam, 0.5 mg of clonazepam and 1 mg of risperidone for presumed exacerbation of psychosis. Over the following 6 hours he became increasingly rigid and delirious. CK increased to 1290 IU/L. A tentative diagnosis of NMS was made, even though the patient had remained afebrile to this point. Antipsychotic medications were held, and intravenous hydration with normal saline was instituted.

Following admission, Neurology and Psychiatry both supported the diagnosis of NMS. In addition to aggressive hydration and discontinuation of antipsychotic medication, specific treatment for NMS with bromocriptine 2.5 mg po t.i.d, dantrolene 25 mg intravenously (IV) q6h, and benzodiazepines was commenced. Serum CK peaked at 2032 IU/L on Day 2 as the patient remained delirious with ongoing muscle rigidity. On the third hospital day he developed a fever of 38.2°C. Examination at this time did not reveal any potential source of infection. Severe dysphagia developed on Day 4, requiring nasogastric tube placement for feeding and administration of medications. The patient was subsequently transferred to the intensive care unit (ICU).

Treatment with bromocriptine, dantrolene and benzodiazepines continued in the ICU. By Day 7, the patient's rigidity lessened and vital signs normalized, although the delirium continued. CK and white blood cell (WBC) counts began to normalize. His improvement continued over the following week, and by Day 15 of his hospital stay, Mr. A was transferred from the ICU to a general medical ward. After several days of observation and continued treatment his vital signs remained stable and his mental status improved. CK had decreased to 300 IU/L by Day 21. He was subsequently transferred to a regional psychiatric hospital for further rehabilitation.

Discussion

This case illustrates one of the many clinical presentations possible with NMS. Though the patient initially had several findings suggestive of NMS including mild muscle rigidity, elevation of serum CK, delirium, diaphoresis, leukocytosis and tachycardia, together they did not fulfill the most commonly used criteria set for NMS, resulting in a delay in diagnosis. This delay resulted in further administration of neuroleptic medications and postponed the implementation of specific treatments. The definitive diagnosis of NMS was only made once other features became apparent, including fever, increased muscle rigidity and greater elevations of serum CK. As some of these findings were not present until 2 days after admission, a diagnostic approach that is more sensitive to early or atypical forms of NMS may have facilitated earlier detection and treatment in this case. Employing criteria such as those proposed by Nierenberg and colleagues[4] may have prevented this delay.

https://doi.org/10.1017/S1481803500014421 Published online by Cambridge University Press

Clinicians frequently use Levenson's criteria to make the diagnosis (see Table 1), which failed in this case. Levenson divided the clinical features of NMS into major and minor manifestations.[5] The 3 major manifestations are 1) fever, 2) muscle rigidity and 3) elevated serum CK (>1000 IU/L). The 6 minor manifestations are 1) tachycardia, 2) diaphoresis 3) abnormal blood pressure, 4) tachypnea, 5) leukocytosis, and 6) altered consciousness. In a patient exposed to neuroleptic medications, all 3 major criteria, or 2 major plus 4 minor criteria, are required for a diagnosis of NMS.

Most of the remaining NMS sets of diagnostic criteria are more restrictive than Levenson's and mandate the presence of fever and muscle rigidity for a definitive diagnosis.[1,4–9]

Nierenberg and colleagues' criteria for NMS describe essential, major and minor criteria (see Table 1).[4] Essential criteria as described by Nierenberg and colleagues are 1) recent use of antipsychotic medication, or 2) recent use of other dopaminergic agent, or 3) recent discontinuation of a dopamine agonist. Major criteria are 1) hyperthermia (temperature >38°C without other cause), 2) muscular

Table 1. Comparison of the Levenson[5] and the Nierenberg and colleagues[4] diagnostic criteria for neuroleptic malignant syndrome

Level of diagnostic criteria	Levenson criteria	Nierenberg and colleagues criteria
Essential	Recent use of antipsychotic	Recent use of antipsychotic
		OR
		Recent use of other dopaminergic agent
		OR
		Recent discontinuation of dopamine agonist
Major	Fever	Fever (>38°C) without other cause
	Muscle rigidity	Muscular lead-pipe rigidity
	Elevated CK (>1000 IU/L)	Elevated serum CK (>3 times normal)
		Autonomic instability (2 or more of sweating, tachycardia, elevated or decreased blood pressure)
		Altered consciousness
Minor	Tachycardia	Autonomic instability (incontinence, arrhythmias or 1 of the features under Major criteria not already accounted for)
	Diaphoresis	
	Abnormal BP	
	Tachypnea	Respiratory distress (dyspnea, tachypnea, hypoxia or respiratory failure)
	Leukocytosis	Leukocytosis (>12.0 $\times$ 10^9/L)
	Altered consciousness	EPS (tremor, cogwheeling, dystonia or choreiform movements)
No. of criterion required	3 Major	4 Major
	OR	OR
	2 Major + 4 Minor	3 Major + 3 Minor

BP = blood pressure; CK = creatine kinase; EPS = extrapyramidal symptoms

https://doi.org/10.1017/S1481803500014421 Published online by Cambridge University Press

lead-pipe rigidity, 3) elevation of serum CK (>3 times normal), 4) autonomic dysregulation (two or more of sweating, tachycardia, elevated or decreased blood pressure), and 5) altered consciousness. Minor criteria are 1) other signs of autonomic dysfunction (e.g., incontinence, arrhythmias, or one of the features under major criteria not already accounted for), 2) respiratory distress (e.g., tachypnea, dyspnea, hypoxemia or respiratory failure), 3) leukocytosis (WBC count > 12.0×10^9/L), and 4) additional signs of extrapyramidal symptoms (EPS) (e.g., tremor, cogwheeling, dystonia, choreiform movements). Four major criteria, or 3 major plus 3 minor criteria, are necessary for diagnosis.

Table 2. Differential diagnosis of neuroleptic malignant syndrome (NMS)[1,2,7,9,19]

Neurologic
*Parkinson's disease
*Meningitis
*Encephalitis
Multiple system atrophy (Shy–Drager syndrome)
Epilepsy
Stroke
Space-occupying lesions
Cerebral vasculitis
Metabolic
Hyperthyroidism
Hypocalcemia
Hypomagnesemia
Pheochromocytoma
Psychiatric
*Delirium
*Depression / mania with catatonic features
*Catatonic schizophrenia / psychosis
Substance-induced catatonia
Medication-induced
*Serotonin syndrome
*Extrapyramidal drug reactions
Benign medication side-effects associated with atypical antipsychotics
Rapid withdrawal of dopaminergic medications (e.g., levodopa)
Dopamine depleting medications (e.g., reserpine, tetrabenazine)
Lithium toxicity
Allergic drug reactions
Substance-induced / toxic
*Anticholinergic poisoning
Cocaine intoxication
Phencyclidine intoxication
Alcohol / benzodiazepine withdrawal
Strychnine poisoning
Other conditions
*Heat stroke
Malignant hyperthermia
Acute intermittent porphyria
Systemic lupus erythematosus
Tetanus
Botulism

*Common causes of NMS-like symptoms

Our patient would have been diagnosed correctly as having NMS if we had used Nierenberg and colleagues' criteria. He displayed rigidity, altered consciousness, tachycardia, diaphoresis and elevated serum CK, thereby fulfilling 4 of the major criteria. This patient also had tremor, incontinence and leukocytosis, therefore fulfilling 3 of the minor criteria and providing further support for the diagnosis. Adityangee and coworkers[10] have provided a detailed review of other diagnostic criteria proposed for NMS.

Diagnosing NMS poses a challenge when a patient with this disorder presents without marked abnormalities of temperature or muscle tone.[2,3,6] In a review of 115 cases of NMS by Addonizio and associates[11] it was observed that EPS preceded fever in 59% of cases.[11] A concurrent development of fever and EPS appeared in only 23%, and 9% had no muscle rigidity. Delayed onset or absence of fever has also been reported with NMS.[12–14] Muscle rigidity may be less common in cases of NMS associated with atypical antipsychotics. The prevalence of EPS in NMS associated with atypical antipsychotics has varied between 78% and 88%.[2,3] In approximately 10%–40% of cases either fever and rigidity will both be attenuated or only 1 will be present.[3,5,11] When such hallmark symptoms are absent, the clinician may mistakenly diagnose an exacerbation of a primary psychiatric disorder, extrapyramidal effects of medications or delirium secondary to neurological, infectious or other medical conditions, thereby delaying diagnosis.[1,2,5,7] The timely and accurate diagnosis of NMS avoids further exposure to neuroleptic medications and allows early initiation of appropriate treatment.

Due to its heterogeneity in presentation, it has been suggested that a neuroleptic toxicity spectrum exists with *forme fruste* or mild EPS at one end and full-blown NMS at the other.[4,15,16] Such a construct may be useful as mild EPS may represent incipient or prodromal NMS in some patients. NMS-like reactions or acute changes in the medical status of patients treated with antipsychotic medications should be considered as "NMS until proven otherwise." Even in its early stages NMS may be a "malignant" disorder. It continues to carry mortality rates between 7%

https://doi.org/10.1017/S1481803500014421 Published online by Cambridge University Press

and 11% despite increased understanding of its risk factors and etiology.[2,11,17]

Several neurological, metabolic and substance or medication-induced disorders are important to consider in the differential diagnosis of NMS (Table 2). Distinguishing between serotonin syndrome and NMS can be particularly problematic as the 2 disorders have several features in common (Table 3). The serotonin syndrome may present with fever, muscle abnormalities, delirium, tremor, autonomic instability and elevations of serum CK.[18] The presence of diarrhea and myoclonus in a patient with NMS-like symptoms should prompt the clinician to consider serotonin syndrome as the etiology as opposed to NMS. A history of exposure to medications that increase serotonergic activity as opposed to neuroleptic medications may the only distinguishing feature on history and examination, although patients are frequently treated with both neuroleptic medications and serotonergic agents.

The pathophysiology of NMS is complex and poorly understood. Dopamine receptor blockade in the pre-optic anterior hypothalamus along with sustained muscle contraction are implicated in hyperthermia associated with NMS.[1,2,11,14] Muscle rigidity and subsequent rhabdomyolysis may be caused by D_2 receptor blockade in the nigrostriatal pathways.[1,2] Autonomic dysregulation in NMS is thought to be secondary to hypothalamic and basal ganglia dysfunction as well as dopamine antagonism in sympathetic and spinal pathways.[1,14] NMS may also occur following rapid withdrawal of dopaminergic agents used to treat Parkinson's disease, further supporting the central role of a

Table 3. Comparison of features, associated medications and management for neuroleptic malignant syndrome and serotonin syndrome[1,19,21]

Variable	Neuroleptic malignant syndrome	Serotonin syndrome
Features common to both disorders	Fever	Fever
	Delirium	Delirium
	Autonomic instability	Autonomic instability
	Tremor	Tremor
	Diaphoresis	Diaphoresis
	Elevated CK	Elevated CK
Distinguishing features	Lead pipe or cogwheel rigidity	Myoclonus
		Hyperreflexia
		Diarrhea
Associated medications	Typical antipsychotics *(e.g., haloperidol, loxapine)*	SSRIs *(e.g., fluoxetine, paroxetine)*
	Atypical antipsychotics *(e.g., clozapine, risperidone, quetiapine, olanzaqpine)*	SNRIs *(e.g., venlafaxine)*
	Metoclopropramide	Tricyclic antidepressants *(e.g., amitriptyline, nortriptyline)*
	Levodopa withdrawal	MAOIs *(e.g., moclobamide, phenylzine)*
Management	Discontinue offending medications	Discontinue offending medications
	Hydration / supportive measures	Hydration / supportive measures
	Bromocriptine	Cyproheptadine
	Amantadine	Methylsergide
	Dantrolene	Chlorpromazine
	Electroconvulsive therapy	

CK = creatine kinase; MAOI = monoamine oxidase inhibitor; SNRI = serotonin/norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

https://doi.org/10.1017/S1481803500014421 Published online by Cambridge University Press

relative hypodopaminergic state in the pathogenesis of the disorder.[1,2,19] Other neurotransmitters implicated in NMS include serotonin, acetylcholine, GABA (γ-aminobutyric acid) and noradrenaline.[1,2] 5-HT_2 receptor blockade and antagonism at dopamine receptors other than D_2 subtypes may account for development of NMS in association with atypical antipsychotics, especially agents which have little D_2 receptor activity such as clozapine.[3,20]

The initial treatment of NMS involves discontinuing antipsychotic medications and maintaining hydration to ensure adequate intravascular volume and to prevent renal failure. As a hypodopaminergic state is thought to be central to the pathogenesis of NMS, dopamine agonists such as bromocriptine have been utilized in treating the condition. The recommended starting dose of bromocriptine is 2.5 mg po t.i.d titrated to a maximum of 10 mg po t.i.d.[1] Dantrolene has been also been used to treat the muscle rigidity associated with NMS. The recommended dosage of dantrolene is 1 mg/kg IV q6h with a maximum dosage of 2.5 mg/kg IV q6h.[1] Electroconvulsive therapy has also been employed successfully to treat NMS in some cases.[1] Studies examining the efficacy of these specific treatments in reducing illness duration and mortality have had conflicting results to date.[1,11]

Employing criteria such as those recommended by Nierenberg and colleagues, which may be more sensitive for early or atypical forms of NMS, could facilitate earlier detection of the disorder and help reduce its considerable morbidity and mortality. Utilizing diagnostic proposals similar to this may increase the number of false-positive diagnoses resulting in unnecessary discontinuation of antipsychotic medications and inappropriate treatment with antidotes. The potential for making such errors is problematic but likely less harmful than allowing for the progression of NMS, which may be fatal. As agreement between diagnostic criteria is poor in any given case of NMS,[21] large prospective studies may help to define the disorder more clearly and lead to more clinically useful and universal criteria.

Conclusion

The neuroleptic malignant syndrome is a rare, possibly life-threatening condition that can be difficult to recognize. Although several diagnostic criteria exist for NMS, most lack sensitivity for early or atypical presentations of the disorder. Utilizing more sensitive sets of criteria may allow for earlier detection and treatment of the condition. Even with more sensitive criteria, a high index of suspicion is still necessary for clinicians to make a prompt and accurate diagnosis in atypical cases. Additional information on NMS is available to medical professionals through the Web site (www.nmsis.org) and toll-free hotline (888 667-8367) provided by the Neuroleptic Malignant Syndrome Information Service.

Acknowledgements: I thank Dr. Joanna Gwiazda, Resident, Department of Psychiatry, Queen's University, Kingston, Ont., and Dr. Susan Finch, Staff Psychiatrist, Queen's University, Kingston, Ont., for reviewing this manuscript.

Competing interests: None declared.

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