ORIGINAL RESEARCH PAPER

Psychiatry

NEUROLEPTIC MALIGNANT SYNDROME VS SEROTONIN SYNDROME : COMMONALITIES & CONTRASTS

KEY WORDS: differential diagnosis, neuroleptic malignant syndrome, serotonin syndrome

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ABSTRACT

Neuroleptic malignant syndrome (NMS) and Serotonin Syndrome are uncommon but potentially life-threatening adverse reactions associated with Psychotropic medications. Polypharmacy and the similar presentation of SS and NMS make diagnosis of the 2 syndromes problematic.

A MEDLINE search was performed for the period 1970 to 2018 for case reports, review articles, and studies pertaining to SS and NMS.

SS presents as mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia. Similarly, NMS presents as muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability. However, the clinical laboratory profile of elevations in creatine kinase, liver function tests (lactate dehydrogenase, aspartate transaminase), and white blood cell count, coupled with a low serum iron level, distinguishes NMS from SS among patients taking neuroleptic and serotonin agonist medications simultaneously. For both SS and NMS, immediate discontinuation of the causative agent is the primary treatment, along with supportive care. For NMS, dantrolene is the most effective evidence-based drug treatment whereas there are no evidence-based drug treatments for SS.

INTRODUCTION

Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are potentially life-threatening adverse reactions to psychotropics. SS originates from an excess of CNS serotonin (5-HT), usually because of serotonin agonist polypharmacy or drug-drug interactions involving serotonin agonist drugs.In [1] 1991, Sternbach presented the first comprehensive SS review that characterized the presentation of 38 patients drawn from 12 clinical reports. [2] The incidence of SS is unknown because many cases go unrecognized and/or unreported. On the other hand, any drug that is a dopamine antagonist is capable of precipitating NMS, which was first reported as an adverse drug reaction associated with the antipsychotic haloperidol in 1960. [3], [4] NMS frequency estimates range from 0.07% to 2.2%. [5-8] Factors that explain the frequency variance include differing diagnostic criteria, misdiagnosis as SS, duration of antipsychotic exposure, and variable antipsychotic dosing practices. Because of common polypharmacy of serotonin agonist and dopamine antagonist agents among individual mental health patients and the similarity of the presentation in SS and NMS, the diagnosis and treatment of these syndromes can be problematic. Our goal is to sort out the diagnostic and treatment confusion.

Etiology and pathophysiology

SS: Case reports indicate that SS is most likely to occur when serotonin agonist drugs are combined in patient treatment. Specific drug classes and drugs include the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs, ie, venlafaxine, duloxetine), triptans, trazodone, nefazodone, L-tryptophan, meperidine, buspirone, carbamazepine, mirtazapine, tramadol, linezolid, and methylenedioxyme thamphetamine (MDMA or Ecstasy). [9,10]

In 1960, SS was described as an "indolamine syndrome" that was thought to be caused by elevations in serotonin and tryptamine. [11] The syndrome presented in patients receiving an MAOI and L-tryptophan concurrently. [11] Although many theories have been proposed for the mechanism of SS, the most creditable is that excess 5-HT in the CNS, which may occur because of excess precursors of 5-HT and its agonists, increase release of 5-HT, decrease uptake of 5-HT, and/or slow 5-HT metabolism.

NMS : As stated, all dopamine-blocking drugs are capable of precipitating NMS. [5] Even clozapine, an antipsychotic with very low affinity for dopamine-2 (D2) receptors in the nigrostriatal tracts, has been associated with at least 14 cases of NMS. [12] Additionally, the abrupt withdrawal of dopaminergic agonist drugs used to treat Huntington's disease and Parkinson's disease, such as levodopa[16] and amantadine[17] has been shown to produce NMS-like conditions.

Numerous hypotheses have been proposed to explain the pharmacologic mechanisms of NMS. However, distillation of these hypotheses results in 2 divergent explanations of NMS pathophysiology. The first emphasizes CNS neuro transmission aberrations and the role of dopaminergic hypofunction in particular.[18] The second endorses peripheral sympathetic autonomic nervous system hyperactivity as the primary culprit.[19] Regardless, none of the hypothesized mechanisms fully explain the signs and symptoms of NMS. [20]

Risk factors

SS: Specific risks factors for SS have not been identified beyond serotonin agonist polypharmacy, such as the potentially fatal combination of an MAOI and an SSRI. Therefore, simply avoiding serotonin agonist polypharmacy can minimize risk.

NMS. Proposed NMS risk factors include exposure to high-affinity D2 receptor drugs, the presence of psychomotor agitation, the use of long-acting depot antipsychotics, neuroleptic polypharmacy, genetic predisposition, external heat load, sex, age, and history of NMS. Unfortunately, assessing the clinical importance of the many proposed risk factors for NMS is difficult because of the conflicting and uncontrolled data in NMS literature. In many cases, it is not apparent if the risk factors truly are related to NMS or if they are simply a confounding variable resulting from some other aspect of the case.

First- vs second-generation antipsychotics. NMS is associated with both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), simply because they are all D2 receptor antagonists. Early clinical hypotheses that SGAs might be "NMSproof" were unfounded. There are case

reports of SGAinduced NMS. A series of 44 cases of NMS associated with use of the SGAs clozapine, risperidone, and olanzapine concluded that one-third of these cases met stringent criteria for NMS. 21 The SGAs were less commonly associated with a temperature >38°C ($P < .05$) and 40°C ($P < .01$) compared with FGAs. However, the temperature difference may be an artifact, because more recent cases of NMS are diagnosed earlier and do not progress to hyperthermia. It is difficult to determine if the incidence of NMS will be reduced with the increased use of SGAs because comparative trials would require at least 500 exposures to detect a single case of NMS because of the rarity of its occurrence.

Antipsychotic dose and intramuscular antipsychotics vs psychomotor agitation. Higher doses of antipsychotics are a risk factor for developing NMS. Affected patients usually are exposed to higher antipsychotic doses titrated upward at a faster than normal rate, oftentimes as multiple intramuscular (IM) injections in agitated patients. 2 case-control studies reported a correlation between psychomotor agitation and NMS. [20] This may be a classic case of the logical fallacy that correlation proves causation. The studies indirectly demonstrate that agitated patients were administered significantly higher doses of antipsychotics, thereby increasing the probability of developing NMS.

Antipsychotic potency. Although it has been suggested that high-potency antipsychotics such as haloperidol vs low-potency antipsychotics such as chlorpromazine are a risk factor for developing NMS[23] this hypothesis remains to be proven. The suggestion likely is related to the clinical observation that haloperidol is more commonly prescribed for agitation than chlorpromazine because of the latter agent's dose-limiting side effect of orthostatic hypotension.

Concomitant medications. Not surprisingly, more than one-half of reported NMS cases involved concomitant psychotropics. [26] Of particular interest is the antipsychotic-lithium combination, which was thought to predispose patients to NMS. Two case-control studies failed to confirm that the antipsychotic-lithium combination is associated with increased NMS risk.[26]

Malignant hyperthermia. Despite the clinical similarities between NMS and malignant hyperthermia (MH), little evidence supports a relationship between these disorders.

Studies have failed to confirm the other proposed risk factors of age, sex, external heat load, and use of depot antipsychotics. NMS has been reported in all age groups, 20 with 55 cases of NMS reported in children. 32-34 Clinical presentation was similar to adults. The postulation that men are more likely than women to experience NMS, although unproven, may be indirectly related to men usually receiving a larger IM dose when agitated, the only legitimate risk factor that appears to be sustained after rigorous scrutiny is the exposure of affected patients to rapidly escalating neuroleptic doses.

Clinical presentation

SS: SS varies significantly among patients in its clinical presentation. It was not until 1991 that the term serotonin syndrome appeared in medical literature.[2] In a report of 12 SS cases, Sternbach[2] categorized the presenting signs and symptoms into the 3 general areas of mental status changes, autonomic nervous system disturbances, and neurologic manifestations. Mental status changes, including mood changes and a clouded sensorium, were observed in the majority of cases (82%), whereas restlessness and agitation were seen in the minority of cases (28%). Autonomic disturbances included tachycardia, diaphoresis, labile blood pressure, shivering, tachypnea, mydriasis, and sialorrhea. Hyperthermia occurred in 34% of cases and was associated with increased severity. Neurologic manifestations included tremor, myoclonus, hyperreflexia, ankle clonus, muscle rigidity, and ataxia.

Laboratory abnormalities were identified as nonspecific or secondary to complications of the syndrome. Leukocytosis occurred in 8% of cases. Rhabdomyolysis occurred in 27% of cases and was associated with increased creatine kinase (CK) levels secondary to muscle rigidity and damage. Rhabdomyolysis advanced to myoglobinuria-induced renal failure in 4% of the cases. Six cases presented with elevated serum hepatic enzymes; 3 were fatal. 37

NMS: Similar to SS, there is substantial variation in NMS clinical presentations. Most, but not all, NMS patients exhibit the 4 cardinal symptoms: muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability. "Lead pipe" rigidity is the most common neurologic finding, but rigidity may present in a less severe form, such as akinesia, dyskinesia, waxy flexibility, or cogwheel rigidity. Fever or hyperpyrexia usually exceeds 38°C and occasionally exceeds 41°C. Mental status changes include stupor, coma, delirium, and catatonia. Autonomic instability presents as tachycardia and fluctuations in blood pressure, with or without respiratory distress.

The extreme skeletal muscle rigidity resulting in muscle necrosis explains the commonly observed elevations in CK, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). [36] In cases of severe muscle damage, rhabdomyolysis and myoglobinuria may lead to renal failure. Low serum iron levels are associated with NMS.[40] Iron is a cofactor for tyrosine hydroxylase, the enzyme that mediates the rate-limiting step of catecholamine synthesis. Therefore, an iron deficiency should result in decreased synthesis of dopamine, which would be exacerbated by dopamine antagonist drugs.[41]

The diagnostic confusion associated with differentiating NMS from SS stems from the 4 cardinal NMS symptoms of muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability also being present, although to a lesser degree of severity, in SS patients. This issue becomes a diagnostic dilemma in patients simultaneously receiving serotonin agonist and dopamine antagonist drugs. The overlap of signs and symptoms confuses the differential diagnosis, whereas the clinical laboratory results are enlightening. A laboratory profile that includes elevated low serum iron, proteinuria, CK, LDH, AST, and leukocytosis occurs in ≥75% of NMS cases. Therefore, it is recommended that particular attention be given to the laboratory data during the differential diagnosis of NMS and SS.

Course

The serotonin drug agonist polypharmacy insult that precipitates SS travels a transient course usually lasting <1 week and can resolve spontaneously despite continued serotonin agonist exposure. However, although rare, fatalities can result from myoglobinuria-induced renal failure, generalized seizures, and disseminated intravascular coagulation.

NMS usually occurs 1 to 2 weeks after the start of therapy or after a significant and abrupt increase of the antipsychotic dose. The frequency of mortality resulting from NMS is difficult to calculate. Predictors of mortality were myoglobinuria (47%) and rhabdomyolysis (56%).

Differential diagnosis

Similar to all drug toxicity reactions, SS and NMS are diagnoses of exclusion. Disorders to be ruled out include infection, seizure, acute lethal catatonia, MH, and anticholinergic drug intoxication. Given the similarity in presentation and symptoms of NMS and SS, the most effective

approach to distinguishing between these syndromes is to obtain an accurate medication history. Medication histories that are positive for both serotonin agonist and dopamine antagonist drugs are problematic. However, more severely ill patients should lead the clinician to suspect NMS rather than SS.

Radomski et al developed a second criterion for SS.[44] After ruling out psychiatric, infectious, metabolic, endocrine, or toxic causes, the diagnosis requires the presence of ≥4 major symptoms or 3 major and 2 minor symptoms after addition or dosage increase of a serotonergic agent to an established serotonergic treatment. Major symptoms include consciousness impairment, elevated mood, coma, myoclonus, tremor, shivering, rigidity, hyperreflexia, and fever. Minor symptoms include restlessness, insomnia, impaired coordination, mydriasis, akathisia, and tachycardia. Lastly, the clinician must ensure that there was no initiation or dosage increase of antipsychotic treatment before symptom presentation. The most recent set of diagnostic criteria for SS are the Hunter Serotonin Toxicity Criteria.[45] The Hunter criteria require one of the following features or groups of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature >100.4°F, and ocular or inducible clonus.

There are various sets of criteria to aid in the diagnosis of NMS.[46] These are primarily useful as a research tool to help assure consistent diagnosis of NMS. However, the clinical diagnostic standard is set by DSM-IV-TR criteria. For a diagnosis of NMS [47] the required criteria are the development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic/ antipsychotic medications not caused by other substances, medical conditions, or mental disorders. Additionally, ≥2 of the following symptoms must be present: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, labile blood pressure, leukocytosis, and evidence of muscle injury (elevated CK). 47 The DSM-IV-TR criteria are useful in differentiating NMS from SS.

Diagnostic considerations. By contrasting the NMS DSM-IV-TR criteria with the 3 sets of SS criteria, the following clues to the differential diagnosis emerge. Severe rigidity is suggestive of NMS, whereas any form of myoclonus suggests SS. Dramatically increased CK and WBC counts and low serum iron levels are laboratory findings more likely indicative of NMS, whereas no laboratory findings are particularly helpful for identifying SS. Gastrointestinal symptoms of nausea, vomiting, and diarrhea are more likely to be indicative of serotonin hyperactivity, whereas these findings usually are not seen with NMS. Finally, changes in vital functions and mental status are common to both disorders, limiting the value of these changes in differential diagnosis.

Treatment

SS. Non-evidence-based symptomatic treatment agents include dantrolene for hyperthermia induced by muscle contraction. Signs and symptoms of SS usually resolve within 1 week of discontinuing or reducing the dose of the causative drug. Case reports theorize that cyproheptadine, a serotonin and histamine antagonist, is a potentially effective antidote.[48] Symptomatic treatment agents include dantrolene for hyperthermia induced by muscle contraction, benzodiazepines for muscle rigidity, anticonvulsants for seizures, and appropriate cardiac medications for labile blood pressure. Propranolol and cyproheptadine also were suggested as adjunctive therapy, along with ventilation for neuromuscular paralysis and dialysis for kidney failure in severe cases.

NMS. NMS becomes a self-limiting condition after the offending agent has been discontinued. Most sources suggest that NMS will resolve completely with supportive care within 1 to 2 weeks unless a depot antipsychotic is involved.[21]

Supportive care. Discontinuation of the causative agent is the single most important NMS treatment intervention. As-needed supportive measures of fluid replacement, fever reduction, and support of cardiac, respiratory, and renal function are indicated. NMS-induced hyperthermia may be difficult to treat using traditional methods. Endovascular and external cooling techniques for patients who fail antipyretic medications has been proposed.[50]

Pharmacologic treatments. Dopamine agonists and skeletal muscle relaxants are the 2 most common pharmacologic treatments for NMS.Dopaminergic drugs such as bromocriptine or amantadine are used to counteract the dopamine blockade that produces the NMS symptoms. Dantrolene is a skeletal muscle relaxant used to decrease rigidity and, possibly, fever.

Electroconvulsive therapy (ECT). There are 2 case reports that consider the effectiveness of ECT for NMS.[52] Because ECT effectively treats acute lethal catatonia (ALC), it stands to reason that ECT might effectively reverse skeletal muscle rigidity in NMS. The authors recommended ECT for severe NMS cases in which there is a high risk of complications, dysphoria with psychotic features is the primary disorder, and catatonia (muscle rigidity) is the major symptom. Although controversial, the use of anesthetic agents in NMS patients is feasible. Trollor and Sachdev noted that a muscle relaxant, usually succinylcholine, was used in 50% of cases.

Treatment recommendations. Bromocriptine and dantrolene are the 2 most widely used specific treatments for NMS. Bromocriptine, an inexpensive oral drug, directly opposes the dopamine effects of antipsychotics. However, this action may worsen a psychotic patient's mental status. Injectable dantrolene is reserved for patients who cannot take oral medication; a switch to oral dantrolene should be made as soon as possible. The most serious adverse effect of dantrolene is severe hepatotoxicity. Although rare, it may occur after prolonged exposure to high dosing. There is no evidence that combining ≥2 specific treatments improves response. Therefore, combinations are recommended only if a single agent has failed to produce a response.

Rechallenge

SS. There are no data regarding rechallenging a patient who has recovered from SS.

NMS. Patients with a history of NMS have a 30% to 50% risk of recurrence after antipsychotic rechallenge.[56] There is a strong inverse correlation between time to recurrence of NMS symptoms and time of antipsychotic rechallenge, according to a review of 41 cases. [56] If the antipsychotic was reintroduced within 5 days of resolution of the initial episode of NMS, the recurrence rate was 63%, whereas if >5 days had elapsed, the recurrence rate decreased to 30%. Of interest, 4 of 7 cases were successfully rechallenged using the same antipsychotic that initially caused NMS. It has also been reported that there is a higher recurrence rate if rechallenge occurs before resolution of NMS symptoms. [54] Caroff and Mann found that if a patient was switched to a low-potency antipsychotic (chlorpromazine, thioridazine, etc.), NMS recurrence rate decreased from 30% to 15%.[24] Likewise, rechallenges were more likely to be successful if a lower dose of antipsychotic was used.

Most NMS patients require continued antipsychotic treatment. Approaches to preventing recurrence of NMS include reassessment of the indication for the antipsychotic, waiting 2 weeks after resolution of NMS before rechallenging, use of a different subclass of antipsychotic and/or an antipsychotic with a different potency, and rechallenge with the lowest possible dose with a slow titration. Alternative treatments for

agitation, such as benzodiazepines, should be considered. Benzodiazepines may be effective alone for agitation or, if given in combination with an antipsychotic, also may allow for lowering of the antipsychotic dose. Finally, avoiding long-acting depot antipsychotics in patients with a history of NMS is advised.

CONCLUSIONS

SS presents as mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia. Similarly, NMS presents as muscle rigidity, hyperpyrexia, mental status changes, and autonomic instability. However, the clinical laboratory profile of elevations in CK, liver function tests (LDH, AST), and WBC, coupled with a low serum iron level, distinguishes NMS from SS among patients taking neuroleptic and serotonin agonist medications simultaneously. For both SS and NMS, immediate discontinuation of the causative agent is the primary treatment, along with supportive care. For NMS, dantrolene is the most effective drug treatment. A 2-week washout of neuroleptic medication minimizes the chance of recurrence.

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