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Serotonin syndrome and neuroleptic malignant syndrome: A case report of intersecting symptomatology

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Abstract

Introduction: Serotonin syndrome and neuroleptic malignant syndrome are caused by 2 distinct pathologies; however, the clinical presentation associated with both syndromes share many features.

Methods: We describe a 56-year-old male patient who presented to our facility with seizures, leukocytosis, fevers, extremity hyperreflexia, and signs of autonomic dysfunction as evidenced by cardiovascular instability. The patient was noted to be taking vortioxetine, trazodone, lamotrigine, lurasidone, and carbidopa-levodopa as outpatient medications for his depression, an unspecified mood disorder, and Parkinson disease. Following a robust workup and failure of other therapies, all serotonergic and dopaminergic medications were held, and the patient was tried on cyproheptadine for serotonin syndrome, which led to the cessation of fevers. Bromocriptine was added to the regimen, which led to the resolution of the remainder of the patient's symptoms.

Results: The overlapping symptomatology of several key diagnostic criteria for both serotonin syndrome and neuroleptic malignant syndrome as well as their nature as diagnoses of exclusion require an evaluation of the patient's aggregate improvement following targeted pharmacologic strategies for both syndromes. The efficacy of both cyproheptadine and bromocriptine when administered concomitantly support the concurrent pathologies.

Discussion: Clinicians at the bedside must be cognizant of the potential for clinically relevant drug-drug interactions that may present with overlapping pathologies.

Keywords: serotonin syndrome, neuroleptic malignant syndrome, medication safety, adverse drug effect, clinical pharmacy

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Background

The nature of critical illness requires that clinicians be cognizant of the potential for overlapping pathologies, especially when a singular diagnosis fails to account for all facets of a patient's presentation or when dealing with diagnoses of exclusion. This acknowledgement is of even greater importance when evaluating drug-induced syndromes and the implications of drug-drug interactions, which are attributed in harming up to 5 million inpatients and causing up to 220,000 emergency department visits annually.[1,2] Whereas many examples of drug-drug interactions and associated medical issues exist or are postulated

TABLE 1: Distinguishing characteristics and diagnostic criteria for serotonin syndrome and neuroleptic malignant syndrome[3,7,8,11,19]

Disorder	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Causative medications	Serotonergic agents (drug interaction or overdose)	Dopamine antagonists (idiosyncratic reaction)
Course of disorder	Rapid onset and resolution (within 24 to 72 hours)	Prolonged onset and resolution (days to weeks)
Symptoms	Agitation, dilated pupils, diaphoresis, hyperthermia, tachycardia, high blood pressure, gastrointestinal upset, seizures Neuromuscular findings: hyperreflexia, tremors	Altered mental status, autonomic dysfunction, hyperthermia, elevated creatine kinase concentrations Neuromuscular findings: severe muscle rigidity or "lead pipe" rigidity
Diagnostic criteria	Hunter criteria Patients must be taking a serotonergic medication and meet at least one of the following criteria: Spontaneous clonus Inducible clonus with agitation or diaphoresis Ocular clonus with agitation or diaphoresis Tremor with hyperreflexia Hypertonia with hyperthermia (temperature > 100.4°F (38°C)	Levenson criteria Presence of 3 major or 2 major and 4 minor signs indicate a high probability of NMS: Major criteria Fever Rigidity Elevated CPK Minor criteria Tachycardia Abnormal arterial pressure Altered consciousness Diaphoresis Leukocytosis

in the literature, one such case is that of serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS).

SS is a preventable yet potentially life-threatening adverse drug reaction precipitated by increased serotonergic stimulation, which can occur with any medication that directly or indirectly increases serotonin neurotransmission.[3] SS is predominantly associated with antidepressants, such as selective serotonin reuptake inhibitors, selective serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. However, other medications and medication classes are also implicated in this syndrome, such as opioid analgesics, antiemetics, and certain antibiotics.[3–6] Whereas SS may occur at therapeutic doses of these agents, the risk is increased with drug-drug interactions that lead to further serotonin release and accumulation or increase in its duration of activity. Management of SS requires prompt discontinuation of all proserotonergic agents and providing the patient with supportive care. Treatment with serotonin antagonists, such as cyproheptadine, may also be beneficial in managing cardiovascular, thermoregulatory, and diaphoretic symptoms and are typically utilized in moderate to severe presentations, whereas benzodiazepines may be employed to mitigate seizure risks and muscle rigidity.[9,10]

Although SS and NMS share similarities in presentation, precipitating medications and onset of symptom development are main distinguishing factors between the 2 disorders and can be reviewed in Table 1.[3,7,8] NMS is an uncommon but severe idiopathic adverse drug reaction that correlates with a disruption in dopamine function caused by dopamine antagonism.[11–13] Whereas NMS is predominantly associated with high potency, first generation antipsychotics, it may also occur with second generation antipsychotics. Additional risk factors for developing NMS include high antipsychotic doses, the use of multiple antipsychotic agents or other medications such as antidepressants and mood stabilizers, rapid parenteral administration of antipsychotics, male gender, and older age.[14] Management of NMS involves prompt discontinuation of all dopaminergic agents along with supportive care.[15] The administration of a dopamine agonist, such as bromocriptine, may be considered in moderate-to-severe patient cases, and benzodiazepines may also be employed as a temporizing agent against muscle rigidity. The following case describes a patient who presented with clinical manifestations of both SS and NMS who responded to a combination of pharmacologic agents used in the treatment of both drug-induced syndromes.

Patient Case

Patient consent was obtained with regards to the following case. We present a 56-year-old Caucasian male (170 cm, 80 kg) who was initially found unresponsive by his wife and was brought to an outside emergency department. His oxygen saturation was 70% on room air, and he was having a seizure. The patient was intubated, given 5 mg of intravenous (IV) midazolam, was loaded with 1500 mg IV phenytoin, and initiated on 100 mg of IV fosphenytoin every 8 hours thereafter. Decorticate posturing with roving eye movements were appreciated. En route to our facility, the patient had significant episodes of bradycardia and received 20 mcg of push-dose IV epinephrine and 0.5 mg of IV atropine. The patient arrived to our facility with significant extensor posturing. Initial imaging was unremarkable. A

TABLE 2: Past medical history and associated medications

Medical Diagnosis	Comments	Associated Medications
Neurologic and Psychiatric Conditions		
Traumatic brain injury	Fall from 10 feet approximately 8 years prior to admission	—
Chronic pain	Associated with fall incident	Oxycodone/acetaminophen, gabapentin, baclofen
Anxiety and depression	—	Trazodone, vortioxetine
Mood disorder, unspecified	Unspecified	Lurasidone, lamotrigine
Parkinson disease	Diagnosed 6 weeks prior to admission	Carbidopa/levodopa
Cardiovascular and Metabolic Conditions		
Hyperlipidemia	—	Atorvastatin, fenofibrate, icosapent ethyl
Coronary artery disease	Status-post 3 stents drug-eluting stents 6 years prior to admission	Aspirin
Cardiovascular disease	—	Carvedilol, furosemide
Hypertension	—	Amlodipine
Type II diabetes mellitus	—	Metformin, insulin glargine, insulin lispro

review of the patient's relevant past medical history and home medication regimen can be reviewed in Table 2.

The patient was admitted to the neurocritical intensive care unit and was found to have a complicated physical exam that precluded the attending physician from performing an adequate mental exam. The patient's ankles and lower extremities were found to be hyperreflexive. In addition, the patient exhibited signs of autonomic dysfunction with systolic blood pressures rapidly fluctuating from as low as 90 mmHg to 260 mmHg. Though the patient's creatine kinase was within normal limits at 78 units/L, the patient did present with a leukocytosis of 18.8 $\times$ 10^3 cells/mm^3 and two fevers of 38°C and 38.6°C, respectively. A lumbar puncture ultimately revealed a normal cerebrospinal fluid study. Interestingly, the patient's urine drug screen was found to be positive for benzodiazepines, cannabinoids, oxycodone, and methadone despite his wife's assurance that he was not using either cannabinoids or methadone and the sample being obtained after the administration of midazolam. The urine drug screen results were ultimately attributed to a presumed false positive screening associated with the use of aspirin and vortioxetine.[16–18] Other considered, but ultimately excluded, diagnoses included substance withdrawal, hypoglycemia, and stimulant usage.

Despite supportive measures, including broad-spectrum antibiotics, an array of imaging studies and laboratory tests, the patient remained essentially unchanged for the first 48 hours of admission. A host of potential etiologies were considered, including Bickerstaff encephalitis, Miller Fisher syndrome, NMS, and SS. Of note, all dopaminergic and serotonergic medications were held since admission. In an effort to either treat or exclude SS, the patient was challenged with cyproheptadine 12 mg by mouth once followed by 6 mg by mouth every 6 hours for 3 doses for a total of 24 hours, which led to the resolution of fevers but none of the other symptoms exhibited by the patient. The patient was experiencing bouts of emesis and high gastric residual volumes, necessitating the use of this dosing schedule as opposed to the more traditional 2 mg by mouth every 2 hours. Following the marginal success of that therapy, the patient was subsequently challenged with bromocriptine 5 mg by mouth every 6 hours in an attempt to rule out or treat NMS. The patient responded to this therapy and experienced a resolution of his lower extremity hyperreflexia. The patient's blood pressure normalized over the course of 72 hours, and the patient was ultimately transferred out of the neurocritical care unit; a general neurology hospitalist team assumed his care. The patient was ultimately discharged to home in stable condition after 6 days in the hospital with his discharge diagnosis being listed as both SS and NMS.

Discussion

Given the multitude of overlapping symptoms exhibited by this patient, evaluation with appropriate diagnostic criteria algorithms may be able to appropriately identify the syndromes and assist with their management. The diagnostic criteria and precipitating medication classes evaluated in Table 1 support a diagnosis of both SS and NMS according to the Hunter and Levenson Criteria, respectively, which are employed by our institution as the standards of patient evaluation for SS and NMS.[11,19] We acknowledge that other diagnostic tools and criteria exist, which presents a complicating factor in the understanding of the intricacies of this patient case. To reference Gurrera's criteria, which were developed on the basis of consensus among international experts in the field, NMS is a probable diagnosis given the patient's hyperthermia, rigidity, and autonomic lability.[13] The patient's fevers and hyperreflexia in the lower extremities are consistent with SS. Supporting both diagnoses, the patient's

blood pressures normalized after 72 hours. An evaluation with the Naranjo algorithm indicates that an adverse drug event was probably responsible for this patient's symptoms based on the offending agents, the timeline to resolution, and the use of a targeted reversal strategy.[20]

Pharmacologic augmentation with agents of different mechanisms, such as antidepressants, antipsychotics, antiepileptics and lithium, is common practice in the management of mood disorders, highlighting the importance of monitoring patients for significant drug-drug interactions and recognizing applicable drug-induced presentations. The patient from this report was on trazodone and vortioxetine, both of which are considered serotonin modulators due to exhibiting mixed serotonergic effects in addition to inhibition of serotonin reuptake: trazodone through 5-HT2A antagonism and vortioxetine through 5-HT1A agonism and 5-HT3 antagonism.[21,22] This combination regimen may have contributed to the patient's presentation with SS-induced seizures and subsequent signs and symptoms.

When investigating other medications from the patient's history, the patient was taking lurasidone and more recently initiated on carbidopa/levodopa for new onset Parkinson disease, both of which are medications associated with alterations in dopamine function. Lurasidone is a second-generation antipsychotic with mixed serotonin-dopamine antagonist activity, which is believed to be the mechanism behind its potential for precipitating NMS and may also have contributed to SS.[23,24] Levodopa, a precursor to dopamine, is utilized in the treatment of Parkinson disease. As a dopamine agonist, carbidopa/levodopa has been linked to NMS in the setting of abrupt discontinuation or rapid dose reduction.[12,25] It was unclear whether such dose titrations were implemented or if withdrawal had occurred in this patient prior to the presentation. However, the timing of presentation relative to the initiation of this dopamine-altering medication aligns with the expected onset of NMS, possibly implicating the Parkinson medication.[7]

Another potential factor is the antiepileptic drug lamotrigine, which exhibits its effect via inhibition of sodium channels, ultimately inhibiting the excitatory neurotransmitter glutamate. The mechanism by which lamotrigine contributes to NMS is unknown but may be attributed to its involvement with the GABAergic system, another neurotransmitter theory surrounding NMS.[26] Last, the concurrent use of antidepressants and dopamine-altering medications in this patient poses a significant risk for both SS and NMS as both drug classes can potentiate the effects of the other, leading to these adverse drug reactions.[14]

Conclusion

To our knowledge, we present one of the only published case reports detailing concomitantly managed SS and NMS. The patient's responsiveness to treatment modalities and demonstrated clinical diagnostic symptoms for each pathology supports our position. Clinicians must be vigilant in evaluating drug-induced syndromes and adverse drug effects at the bedside, especially in patients on multiple medications that may predispose them to deleterious outcomes.

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