Neuroleptic Malignant Syndrome vs Serotonin Syndrome: Can They Be Distinguished Without an Underlying Etiology?

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The potentially serious complications for patients with neuroleptic malignant syndrome and serotonin syndrome cannot be underplayed by mental health clinicians, patients, and their families. The authors discuss clinical similarities and diagnostic and treatment approaches to the 2 syndromes.

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are rare but potentially fatal conditions associated with the treatment of psychotropic medications. Neuroleptic malignant syndrome is believed to be caused by a reduction in dopaminergic activity secondary to drug-induced dopaminergic blockage, whereas SS results from an excess of central nervous system (CNS) serotonin activity, usually because of serotonin agonist polypharmacy or a drug-drug interaction involving serotonin agonist drugs.[1,2] However, the clinical presentations of the 2 syndromes are alike in many ways. Neuroleptic malignant syndrome and SS may be difficult to distinguish if it is not known what medications the patient was taking before the onset of symptoms or whether the patient was taking different medications that could affect both the serotonin and dopamine systems.

In clinical practice many patients are treated concurrently with both dopamine receptor antagonists and agents that increase serotonin activity. Thus, the distinction of NMS and SS may be problematic if these patients develop symptoms that could be attributed to either disorder. This article will discuss the clinical similarities of NMS and SS and the treatment approaches to the 2 syndromes, as well as possible clues that may help to distinguish one from the other.

CASE PRESENTATION

Mr. A, a 28-year-old man with chronic, undifferentiated schizophrenia since his late teens, was evaluated at the psychiatric clinic of the G.V. (Sonny) Montgomery VAMC in Jackson, Mississippi, where he reported auditory hallucinations and paranoia. He also reported feeling hopeless about his future and depressed, because he could not maintain employment. He had stopped taking his medication (risperidone 3-mg daily) 3 months earlier, because he was experiencing adverse effects (AEs) and shortly thereafter hearing voices. The clinic psychiatrist started him on olanzapine 10-mg daily and sertraline 50-mg daily. At a follow-up visit a week later, Mr. A showed an improvement of his mood and reported that his hallucinations had decreased significantly.

Several days later, Mr. A became confused and was found wandering around his neighborhood. He was brought to the hospital by the police. An examination at the hospital revealed his being disheveled and agitated. He was tremulous and diaphoretic. His speech was loud and pressured. His vital signs were the following: heartbeat rate, 110 bpm; blood pressure (BP), 98/62; respiration, 20 breaths/min; and temperature, 102.6°F. An examination of the heart, lungs, and abdomen revealed no additional evidence of pathology. Deep-tendon reflexes were diffusely increased. Muscle tone in the extrem-

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ities was increased. No other physical abnormalities were detected.

Mr. A's orientation was to person and year only. He could not recall the events of recent days. Laboratory findings included a white blood cell count (WBC) of 13,800 cells/mm^3 with a mild left shift. The chemistry survey results were unremarkable, except for the mild elevation of the blood urea nitrogen (BUN) (26 mg/dL)and creatinine (1.3 mg/dL) tests. Creatinine phosphokinase (CPK) level was 402 IU/L. Liver function studies, serum iron level, and thyroid-stimulating hormone results were within normal limits. The urine drug screen was negative, and the computed tomography scan of the head and lumbar puncture findings were unremarkable.

Determining the exact diagnosis for Mr. A's condition was difficult. His symptoms not only could have been considered consistent with NMS related to the recently started olanzapine, but also with SS related to the recently initiated sertraline. Both medications were withheld. He was admitted to an intensive care unit (ICU) and closely monitored and treated with supportive measures. In the ICU he was given intravenous D_5W 0.45% NaCl, requiring 5 liters on the first day. He was given lorazepam as needed for agitation, receiving a total of 4 mg on the first hospital day and 2 mg each on hospital days 2 and 3. After 3 days his confusion and agitation resolved, and he was able to communicate effectively. Laboratory parameters returned to normal ranges, including WBC, 8,700 cells/mm^3; BUN, 19 mg/dL; creatinine, 0.9 mg/dL; and CPK, 190 IU/L.

Intravenous fluids were discontinued, and Mr. A was transferred to a psychiatric unit. Within a few days there, he again complained of auditory hallucinations and depression. He was treated cautiously with ziprasidone and venlafaxine starting at low doses, which were then titrated slowly. He was discharged 2 1/2 weeks later on ziprasidone 80-mg bid and venlafaxine 150-mg daily.

During subsequent clinic visits, Mr. A maintained an euthymic mood. He still experienced occasional hallucinations and paranoia but was not disturbed by his symptoms. He was able to procure and maintain employment at a local grocery store, had no further episodes of agitation or confusion, and experienced no AEs from his current medications.

NEUROLEPTIC MALIGNANT SYNDROME

All dopamine-blocking drugs are capable of precipitating NMS. Neuroleptic malignant syndrome was first described in 1960 during clinical trials with haloperidol. Since then, NMS has been reported to occur with all dopamine-blocking agents, including the newer atypical antipsychotic agents. The abrupt cessation of dopaminergic-agonist drugs used to treat Huntington disease and Parkinson disease may also produce NMS-like conditions.[3]

A large number of cases of NMS have been reported, but many features of the syndrome remain controversial. In a classic case, symptoms of NMS include fever, autonomic instability (BP instability and tachycardia), rigidity, and mental status changes. Medical students sometimes use the mnemonic FARM to recall this constellation of symptoms. Neuroleptic malignant syndrome is frequently misdiagnosed and can be fatal in 5% to 20% of patients if untreated.[4] Risk factors for NMS include young age, male gender, preexisting brain injuries or insults, physical illness, dehydration, rapid escalation of antipsychotic dosage, use of high-potency antipsychotic agents, and use of intramuscular antipsychotic agents.[4] Dehydration is a risk factor not only for NMS, but also for further complications of NMS, explained later.

Neuroleptic malignant syndrome may be a serious disorder. Creatinine phosphokinase may rise to as much as 60,000 IU/L. White blood cell counts are typically in the range of 10,000 to 40,000 cells/mm^3, sometimes with a left shift.[5] Possible medical complications are numerous and can include organ failure, particularly renal failure, possibly resulting from dehydration and from a large amount of myoglobin produced by rhabdomyolysis. Pulmonary aspiration may occur due to dysphagia or obtundation. Respiratory failure may result from aspiration pneumonia or decreased chest wall compliance. Deep venous thrombosis and pulmonary embolus may occur secondary to immobility. Problems with electrolyte imbalance may involve hypokalemia, hyponatremia, or hypernatremia. Other complications that have occurred with NMS include myocardial infarction, congestive heart failure, cardiac arrhythmias, thrombocytopenia, and disseminated intravascular coagulation. Immobility may cause pressure ulcers and related complications. These complications may in some cases result in the death of the patient.[5,6]

According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR), the diagnosis of NMS should be assigned only to patients who develop severe muscle rigidity and elevated temperature while receiving a neuroleptic drug and who display 2 or more of the following signs and symptoms: diaphoresis, dysphagia,

Table. Clues that may help distinguish neuroleptic malignant syndrome and serotonin syndrome when no precipitating agent can be identified[3,5,16,18]

Clinical course
Rapid onset and progression: More likely SS
Rapid resolution: More likely SS
Clinical symptoms
Gastrointestinal symptoms: More likely SS
Shivering: More likely SS
Clinical signs
Severe rigidity: More likely NMS
Myoclonus: More likely SS
Hyperreflexia: More likely SS
Laboratory findings
Severely elevated CPK: More likely NMS
Severely elevated WBC: More likely NMS
Low serum iron levels: More likely NMS

CPK = creatinine phosphokinase; NMS = neuroleptic malignant syndrome; SS = serotonin syndrome.

tremor, incontinence, changes in the level of consciousness, mutism, tachycardia, elevated or labile BP, leukocytosis, and laboratory evidence of muscle injury.[7] Diagnostic criteria developed by Levenson requires 3 major criteria or 2 major and 4 minor criteria to indicate a high likelihood of NMS in the appropriate clinical context. The major criteria proposed are fever, rigidity, and elevated CPK level; the minor criteria are tachycardia, abnormal BP, tachypnea, altered consciousness, diaphoresis, and leukocytosis.[8] Other diagnostic criteria have also been proposed, and the exact criteria most appropriate for usual clinical practice have not been conclusively reached.[9] Clinical symptomology of NMS may vary. Incomplete presentations with only partial symptoms often occur early in the course of the disorder. Atypical forms of NMS also often occur, making the diagnosis more difficult; for example, a patient meeting other criteria for NMS but lacking rigidity or hyperthermia. Such cases are frequently secondary to treatment with an atypical antipsychotic agent.[10]

SEROTONIN SYNDROME

Case reports of patients with AEs secondary to increased serotonin activity began to appear in the 1980s. Serotonin syndrome is characterized by a triad of neuroexcitatory features, including neuromuscular hyperactivity (tremor, clonus, myoclonus, hyperreflexia, and in severe cases, pyramidal rigidity), autonomic hyperactivity (diaphoresis, fever, tachycardia, tachypnea), and altered mental status (agitation, excitement, and confusion).[2] As with NMS, complications may be serious, and there may be significant variations in the clinical presentation. The mortality rate of SS is unknown; the disorder may resolve quickly with removal of the offending agent(s) or may be potentially fatal.[6] Specific risk factors for SS have not been identified beyond serotonin polypharmacy, such as the potentially fatal combination of a selective serotonin reuptake inhibitor (SSRI) and a monoamine oxidase inhibitor (MAOI).[3]

A review by Sternbach with suggested diagnostic criteria was published in 1991.[11] Sternbach proposed criteria that included the occurrence concomitant with the addition of a serotonergic agent to an established medication regimen of at least 3 of the following features: mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, or fever. Additional requirements are that other etiologies (eg, infectious, metabolic, substance abuse, or withdrawal) have been ruled out and that an antipsychotic agent was not started or increased in dosage before the onset of the signs and symptoms.

Other criteria have also been proposed for SS; eg, Radomski proposed that after ruling out other causes there be present 4 or more major symptoms or 3 major and 2 minor symptoms. The major symptoms proposed are impairment of consciousness, elevated mood, coma, myoclonus, tremor, shivering, rigidity, hyperreflexia, and fever; the minor symptoms are restlessness, insomnia, impaired coordination, mydriasis, akathisia, and tachycardia.[12]

The most recent set of diagnostic criteria of SS are the Hunter Serotonin Toxicity Criteria, which require 1 of the following features or groups of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agi-

tation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature >100.4°F, and ocular or inducible clonus.[13]

Serotonin syndrome can result from anything that increases serotonin activity in the CNS, which can occur by a number of mechanisms[14]:

- Inhibition of serotonin uptake: SSRIs; other antidepressants, such as the tricyclics, venlafaxine, trazodone, and duloxetine; amphetamines; cocaine; St. John's wort; meperidine; dextromethorphan; tramadol; and others
- Inhibition of serotonin metabolism: MAOIs; linezolid
- Increases of serotonin synthesis: tryptophan
- Increases of serotonin release: amphetamines; cocaine; fenfluramine; methylenedioxy-methamphetamine
- Increases of serotonin activity: lithium
- Agonist action at serotonin receptors: buspirone; sumatriptan and related migraine medications

Any combinations of the abovementioned medications can increase the risk of SS. Thus, use of many common medications may inadvertently increase the likelihood of the occurrence of the syndrome.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients who may have NMS or SS includes any disorder that can present with any combination of altered mental status, fever, and rigidity.[5] This includes infections of the CNS, drug toxicity, heat strokes, acute dystonic reactions, and other medical issues, such as vasculitis. Besides NMS, rigidity may be a symptom of catatonia, which may be due to several conditions, including schizophrenia (particularly catatonic schizophrenia), that can present with mental status changes and fever. Malignant hyperthermia must be considered when there is a history of recent anesthesia. Anticholinergic toxicity may present with fever, confusion, and hallucinations but usually produces muscular relaxation. Conversion disorder might be a consideration in cases without fever or objective signs.[15]

THE OVERLAP OF NMS AND SS

If one compares the proposed criteria for NMS and SS, a significant overlap of symptoms can easily be seen. Strictly based on the DSM-IV-TR criteria for NMS and on Sternbach's criteria for SS, fever, altered mental status, diaphoresis, and tremor are symptoms common to both disorders. Other proposed criteria for NMS and SS also allow for additional overlap of symptoms. For example, rigidity is required for a diagnosis of NMS by the DSM-IV-TR criteria and is cited as a major symptom for SS in the criteria proposed by Radomski and colleagues.[12]

The overlap in symptoms is particularly notable with NMS secondary to atypical antipsychotics, which often demonstrates incomplete features of the classic NMS presentation and may have features that could also be seen in SS. For example, in an investigation of 17 patients on olanzapine diagnosed with NMS, SS features among the patients included fever (82%), mental status changes (82%), diaphoresis (47%), tremor (35%), agitation (23%), hyperreflexia (18%), incoordination (12%), myoclonus (6%), and diarrhea (6%).[16]

Thus, a patient on a dopamine antagonist and a serotonin agonist who develops part of this constellation of symptoms can pose a diagnostic dilemma. It is worth noting that in many mental health clinics, use of both classes of medications occurs every day. Common dopamine antagonists include risperidone, aripiprazole, ziprasidone, quetiapine, paliperidone, and haloperidol and several older typical antipsychotic agents. Common medications that increase serotonin activity are noted earlier in this article. With the high incidence of psychosis and depression among psychiatric patients, it is a very common occurrence for both classes of medications to be concomitantly prescribed to many patients.

DIAGNOSTIC APPROACH

The diagnostic workup should include routine screening for causes of delirium and a careful history. Particular attention should be paid to any recent initiation or increase in dosage of any dopamine blocking agent or of any drugs that increase serotonin activity. These medications may need to be immediately withheld pending further assessment.

Detailed physical and neurologic examinations should be completed. Laboratory tests should include a chemistry survey, complete blood count, liver functions, thyroid profile, serum CPK, urine myoglobin, and blood and urine cultures. Neuroimaging should be performed to rule out structural and related cerebral etiologies, such as a brain neoplasm or hemorrhage. A chest X-ray, arterial blood gases, and an electrocardiogram may also be indicated. A lumbar puncture should be performed for patients with suspected CNS infections.

DISTINGUISHING NMS AND SS

The difficulty of distinguishing NMS and SS has been well recognized.[1] It has even been proposed that NMS and toxic SS are not truly separate syndromes or entities but are examples of nonspecific, generalized neurotoxic syndromes that share a similar pathophysiology.[17] The varia-

tions and overlap seen in NMS and SS would then represent a broad class of nonspecific acute symptoms of neurotoxicity.

Although NMS and SS are similar in presentation, some clues may be apparent that suggest which disorder is the more likely diagnosis. It must be noted, however, that clinicians should never assume a definite diagnosis of NMS or SS based on the presence or absence of a given finding, because almost any finding could conceivably occur in either syndrome. In many cases, the onset of SS is more rapid (often within hours of the precipitant) and the progression of symptoms more rapid than NMS.[18] Resolution of symptoms may also be more rapid with SS compared with those of NMS. Severe rigidity is suggestive of NMS, whereas myoclonus suggests SS. Hyperreflexia, particularly in the lower extremities, is common in SS.[5] Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, are more likely to be due to serotonin hyperactivity and thus SS.[3] Shivering may be more suggestive of SS, because this symptom seems to be infrequently observed in patients with NMS, at least in those with NMS secondary to atypical antipsychotics.[16]

Laboratory findings may sometimes be helpful in distinguishing NMS and SS. Dramatic increases of CPK and WBC counts are more likely indicative of NMS. Low serum iron levels are also more likely to occur with NMS than with SS.[3] Most other laboratory tests are not helpful in distinguishing NMS and SS. Although useful for ruling out certain underlying causes of delirium, such as structural brain lesions, neuroimaging is of no value for distinguishing NMS from SS, and neurophysiologic tests such as an electroencephalogram or evoked potentials have also not been shown to be helpful.

The search for a definitive diagnostic test continues. Measurement of serotonin and dopamine metabolites may prove useful as a diagnostic adjunct but has yet to be established, and additional research is needed.[19] Clues that may be helpful in distinguishing NMS from SS are summarized in the Table.

TREATMENT APPROACH

The initial treatment of a patient with suspected NMS or SS involves identifying any potential causative agents, ie, any drugs that decrease dopamine or increase serotonin activity that have been recently started or increased in dosage. These medications should be immediately discontinued.

The general approach to such a patient is similar to that of other patients with delirium. Treatment in an ICU or similar setting may be necessary. Urgent medical issues must be promptly identified and addressed and the patient closely observed for the development of any new medical complications. Cardiovascular, respiratory, and renal functions must be strictly monitored. The patient should be provided an environment that is as quiet and nonstimulating as possible. Frequent reorientation and measures using a calm approach may be helpful.

Supportive care is a mainstay of treatment. Intravenous fluids should be given to alleviate dehydration and prevent development of myoglobinuria. Fever and diaphoresis may create electrolyte imbalance, so frequent evaluation of laboratory values may be necessary to determine what maintenance fluids and replacement electrolytes are needed. Aggressive treatment of fever should be initiated by administering antipyretics and physical cooling measures such as cooling blankets. Analgesics should be used to control pain associated with severe muscle rigidity. It should be kept in mind that patients who are delirious may not be able to communicate their discomfort effectively and that untreated pain may worsen a patient's agitation. The patient must be assessed periodically for the development of complications of immobilization, such as pneumonia, thromboembolism, or pressure sores.[4,5,20]

Some evidence suggests that for patients with NMS, compared with supportive treatment alone, bromocriptine or amantadine (which act as dopamine agonists) or dantrolene (which acts directly on skeletal muscle to produce relaxation) may improve symptoms.[4] Based on the overlap in symptoms between catatonia and NMS, treatment with benzodiazepines, such as lorazepam, may be helpful for muscle rigidity.[21,22] However, these drugs can also contribute to worsening delirium, particularly when the underlying medical condition is unknown. In patients with severe treatment resistant NMS, electroconvulsive therapy may be of value.[4] Case reports suggest that cyproheptadine (which acts as a serotonin antagonist) is useful for treating SS.[3]

Most patients with NMS will require resumption of treatment with an antipsychotic agent. Strategies that might help prevent recurrence of NMS include reassessment of the indication for an antipsychotic, waiting 2 weeks after resolution of NMS before rechallenging, using a different subclass of the antipsychotic, using an antipsychotic with lower potency, rechallenging with the lowest possible dose with slow titration, and avoiding long-acting depot antipsychotic agents.[3] There are no data regarding rechallenging a patient who has recovered from SS.

CONCLUSIONS

Serotonin syndrome and NMS are poorly understood neuropsychiatric disorders that share many common features and may be related to each other. In cases without a clear precipitating agent, a careful history and attention to symptomatic details can, in many instances, distinguish the 2 syndromes. Mental health clinicians should be aware of these syndromes, which, although relatively uncommon, may have serious complications.

Patients prescribed antipsychotics should be advised of the risk of NMS and those patients prescribed drugs that increase serotonin activity of the risk of SS. Patients and their families should be provided education about the syndromes they may be at risk for and made aware of symptoms to look for. Any patient under treatment with these medications (and their families) should understand that they should seek medical attention if they develop agitation, confusion, or rigidity, particularly if associated with fever, diaphoresis, tachycardia, or tachypnea. The importance of obtaining rapid medical assessment and treatment should be stressed.

Clinicians prescribing antipsychotics and drugs that increase serotonin activity should regularly monitor their patients for development of AEs, including signs of NMS or SS. Finally, awareness of NMS and SS is needed by other members of the medical community who might encounter these syndromes, particularly emergency department physicians and internists. ●

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