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NEUROLEPTIC MALIGNANT SYNDROME OR SEROTONIN SYNDROME?

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Dear editor,

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are rare, life-threatening, drug-induced disorders. Both syndromes share clinical features, such as pyrexia, hypertonia, autonomic instability, and changes in mental state, making differentiation difficult. Differentiation is important as pharmacologic treatment is dependent on the causative agent, such as antipsychotics or antidepressants.

A 66-year-old man with schizoaffective disorder presented to the emergency room for disturbance of consciousness with high fever. He had been treated with risperidone 4 mg/day and paroxetine 20 mg/day for the past several years, but due to agitation and aggression, risperidone was increased to 6 mg/day three days ago. On arrival, the patient was confused with hypertension of 170/90 mmHg, tachycardia of 120/min, and marked sweating. The muscles in his lower legs were rigid and hyperreflexia in the lower extremities was noted. Blood tests showed increased white blood cell count, C-reactive protein, and creatine kinase, but no physical findings suggestive of infection.

Would this case be NMS or SS? The differential diagnosis between NMS and SS is even more difficult in polypharmacy patients who are taking both antipsychotics and antidepressants. I read with great interest the review article on the differentiation between NMS and SS (Debeljak & Kores Plesničar 2021). They noted subtle differences in the clinical manifestations of impaired consciousness and extrapyramidal symptoms between NMS and SS. The NMS is due to excessive blockade of dopamine D2 receptors, while the SS is due to excess serotonin. Not only a decrease in dopamine but also an increase in serotonin modulates the autonomic nervous system, resulting in autonomic instability such as tachycardia, hypertension, excess sweating, and hyperthermia. As for the change in consciousness, however, a decrease in dopamine leads to stupor, while an excess of serotonin leads to agitation. As for motor function, a decrease in dopamine is manifested as lead pipe phenomenon, while an excess of serotonin is manifested by muscle spasms (Figure 1). Extrapyramidal symptoms of SS may show neuromuscular hyperactivity that closely resembles epileptic seizures (Prakash et al. 2019). Thus, this patient was diagnosed with SS based on hyperreflexia of the lower extremities. Paroxetine was discontinued and risperidone was reduced to the original 4 mg/day, resulted in an improvement of consciousness and muscle tone within a few days.

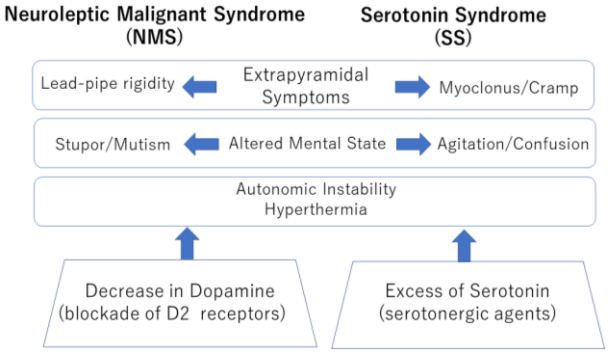

Figure 1. Schematic of similarities and differences between NMS and SS symptoms

This case should be considered NMS based on the prescription pattern of psychotropic drugs, with onset at an increased dose of risperidone. However, features of extrapyramidal symptoms suggested serotonin excess. So why was serotonin excess promoted by increasing doses of risperidone? Risperidone and paroxetine are both mainly metabolized by cytochrome P450 2D6 (CYP2D6) in the liver. Furthermore, paroxetine has the highest inhibitory constant for

the CYP2D6 of all antidepressants (Ki = 0.065-4.65 micromoles) (Nevels et al. 2016). Paroxetine's potent inhibitory effect on CYP2D6 significantly inhibits the metabolism of the CYP2D6 substrates including risperidone and paroxetine, resulting in elevated levels of both risperidone and paroxetine. The addition of risperidone could deprive CYP2D6 and cause a decrease in paroxetine metabolism, resulting in serotonin excess. Recently, it has been reported that concomitant use of antipsychotics and antidepressant agents, which share a common metabolic enzyme, can lead to serotonin excess (Nagamine 2022a). The patient developed SS but was also in a hypodopaminergic state and was at risk for developing NMS, so the risperidone dose was reduced. Not all cases will develop SS or NMS, and the risk is thought to vary according to genetic polymorphisms of serotonin receptors in SS and dopamine receptors in NMS. Genetic polymerphisms in CYP2D6 markedly increase psychotropic drug concentrations under polypharmacy. Although the genetic polymorphism in the present case has not been investigated, it is possible that the patient was a poor metabolizer of CYP2D6. In the future, if personalized medicine is developed, it will be possible to adjust the optimal dosage for each patient, which will lead to the prevention of SS and NMS.

During the COVID-19 pandemic, patients with unknown fever require a careful differential diagnosis, and NMS and SS are differential diseases in febrile patients taking psychotropic drugs (Nagamine 2022b). Psychotropic polypharmacy increases the concentration of each drug because each drug is metabolized by a common metabolic enzyme, making NMS and SS more likely to develop. Increased psychotropic drug concentrations due to drug interactions should be noted, and differences in extrapyramidal symptoms are key to differentiating NMS from SS.

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OPTIMAL DOSAGE OF ANTIDEPRESSANTS IN THE TREATMENT OF BURNING MOUTH SYNDROME

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Dear editor,

Burning mouth syndrome (BMS) is an intractable chronic pain disorder of unknown cause characterized by burning sensation without any organic abnormality in the oral mucosa. Treatment options include antidepressants, benzodiazepines, antipsychotics, anticonvulsants, analgesics, hormone replacement therapy, and psychotherapy, with antidepressants being the most commonly used and effective. BMS patients have difficulty being understood about their pain by their families and health care providers, and tend to be anxious and depressed after the onset of the disease (Sikora et al. 2018). However, antidepressants are effective for BMS not because they improve depressive symptoms. The doses of antidepressants used in BMS treatment are much lower than the doses that produce antidepressant effects and increase side effects in a dose-dependent manner. The most commonly used and proven effective antidepressants for BMS patients in Japan are amitriptyline and aripiprazole. Amitriptyline and aripiprazole used in BMS averaged 10 mg/day and 1.0 mg/day, respectively, with roughly equivalent efficacy, but these doses are less than one-fifth the dose used as an antidepressant (Watanabe et al. 2022). Amitriptyline is a serotonin stimulator and aripiprazole is a dopamine neuromodulator, which have very different mechanisms of action. Given that small doses of antidepressants are effective and that both serotonin and dopamine regulation are equally effective in neurotransmitters, how should we think about the pathogenesis of BMS?

Antidepressants are generally thought to be effective for pain management because they activate the descending pain inhibitory pathway, but does this also apply to BMS patients? Pain stimuli have an ascending circuit that travels upward to the brain and a descending pathway that travels from the cerebral cortex to the spinal cord. The periaqueductal gray matter (PAG) is an important hub that relays the ascending and descending pathways of pain sensation. The PAG accepts not only ascending sensory input from the spinal cord but also information from the limbic system and transmits it descending to the dorsal horn of the spinal cord, inhibiting pain transmission. This descending pain inhibitory pathway is activated by serotonin, noradrenaline, GABA, and dopamine. Since both amitriptyline and aripiprazole act on the descending pain inhibitory pathway, this conventional mechanism may explain the pain-improving effects of antidepressants in BMS. However, it should be difficult for BMS patients to ameliorate pain by activation of the descending pain inhibitory pathway alone, because pain-inducing nociceptive stimuli are not present in the oral mucosa.