

NEUROLEPTIC MALIGNANT SYNDROME AND SEROTONIN SYNDROME- A COMPARATIVE REVIEW

Psychiatry

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KEYWORDS

INTRODUCTION

Neuroleptic Malignant Syndrome- is a rare yet life threatening, idiosyncratic reaction to the use of dopaminergic receptor antagonist medications which is generally presented with fever, muscle rigidity, altered mental status and autonomic dysfunction due to dopamine inhibition.(1)

In the brain, dopamine receptors control movement, emotions, and the reward system. The subventricular zone and hippocampus and dentate gyrus are two locations in the central nervous system where these receptors are found.(2)

NMS was first described by Delay and colleagues in 1960 in the patients who were treated with high-potency antipsychotics.

Antipsychotic medications are mainly used to treat schizophrenia and other psychotic states.

These Drugs are Classified as:

- Typical(1st generation) Antipsychotics like chlorpromazine and haloperidol acts through inhibition of D2 receptors only while
- Atypical(2nd generation) Antipsychotics like olanzapine and aripiprazole act through inhibiting D2 and 5HT2A receptors.
- Cases have been reported in association with antiemetics(like metoclopramide, promethazine, levosulpiride), tricyclic antidepressants and lithium.
- Additionally, the sudden discontinuation of anti-parkinsonian drugs, which effectively reduce the brain's dopaminergic activity, has been linked to NMS.

Serotonin Syndrome

it occurs due an excessive increase in the serotonergic activity throughout the central nervous system which leads to serious and potentially life threatening condition. It is a neurotransmitter that controls behavior, mood, and other physiological functions. The neurotransmitter is produced naturally in the body and can be also found in certain medications like selective serotonin reuptake inhibitors(SSRIs)-citalopram, fluoxetine and serotonin-norepinephrine drugs like desvenlafaxine, venlafaxine, illicit substances and supplements. SS usually is the cause of therapeutic medication use and also accidental interactions between the medications and recreational drugs or an intentional overdose. The symptoms are presented by altered mental status, autonomic dysfunction and neuromuscular excitation.(3)

Etiology

Neuroleptic Malignant Syndrome- Antipsychotic and antiemetic medications that can trigger NMS:

First-generation antipsychotics	Chlorpromazine Fluphenazine Haloperidol Loxapine Mesoridazine Molindone Perphenazine Pimozide Thioridazine Thiothixene Trifluoperazine
Second-generation antipsychotics	Aripiprazole Clozapine Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone

Antiemetics	Domperidone Droperidol Metoclopramide Prochlorperazine Promethazine
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Fig-1-Table-1(4)

Serotonin Syndrome- Medications which modulate the Serotonergic system and may trigger SS:

Increased Serotonin Synthesis	Inhibit Serotonin Metabolism	Increased Serotonin Exocytosis	Increased 5-HT ₁ Activation	5-HT _{2A} Antagonism	Reuptake Inhibition
*Tryptophan	MAO-I	Cocaine	Buspirone	Atypical antipsychotics	SSRI
	*St. John's Wort	Ecstasy (MDMA)	Triptans	Chlorpromazine	SNRI
	Linezolid	Dextromorphan	Ergot Derivatives		
	Tedizolid		Opiates		
	Methylene Blue		LSD		
	Procarbazine		Mirtazapine		
	*Syrian Rue		Trazodone		
			Lithium		

Fig-2-Table-2(5)

Epidemiology

Neuroleptic Malignant Syndrome - The incidence rates for neuroleptic malignant syndrome range from 0.02 to 3 percent among the patients taking antipsychotics or other central dopamine (D2) receptor antagonists (all age groups; some research have found a male:female ratio of 2:1; previous reports have indicated higher incidence rates).

Newer, less powerful antipsychotics may have a lower incidence and less severe symptoms, especially when it comes to clozapine.

NMS manifests in roughly 16% of individuals within 24 hours of starting antipsychotic treatment, 66% within the first week, and less frequently within or after 30 days on consistent pharmaceutical regimens.(6)

Serotonin Syndrome

The incidence of serotonin syndrome in the population following an overdose of selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors is approximately 15%. Patients who have mclobemide poisoning have a relatively high prevalence of SS (about >55%), especially if the medication was taken with another serotonergic substance. The incidence of SS on therapeutic doses of different serotonergic drugs ranges from 0.006% to 25%. Thus, there is a considerable range in the reported incidence of serotonin syndrome worldwide.(7)

Pathophysiology

Neuroleptic Malignant Syndrome- Usage of high potency antipsychotics cause dopamine down regulation in the nigrostriatal pathway which causes muscular rigidity and in hypothalamus it causes hyperthermia and in mesolimbic and mesocortical pathway it leads to altered mental status.(8) It is generally attributed to sudden reduction in central dopaminergic activity due to a D2 receptor inhibition or an abrupt withdrawal of D2 stimulation.

Serotonin Syndrome

May occur as a consequence of the therapeutic medication use, illicit drugs use, or intentional overuse of the drugs. Serotonin toxicity can be

caused by a number of drugs and through different processes. Excessive serotonergic activity at 5-HT receptors centrally and peripherally leads to 1) increase in serotonin synthesis and release, 2) decrease in serotonin reuptake and metabolism, 3) increase in receptor agonism and sensitivity. All these mechanisms lead to altered mental status, autonomic instability and neuromuscular hyperactivity.(9)

Symptoms

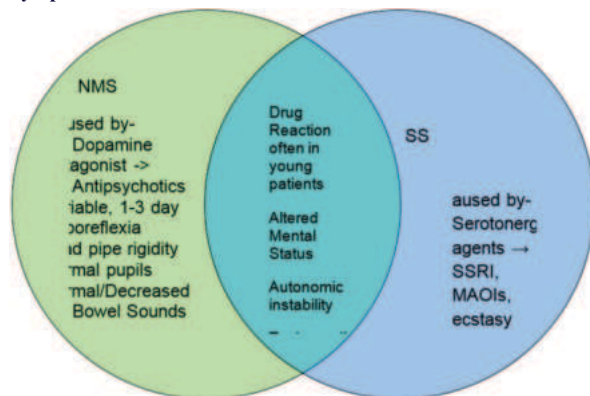


Fig-3

Diagnosis

Neuroleptic Malignant Syndrome- The diagnosis is made on the basis of history of medications and current medications taken by the patient and clinical signs and symptoms the patient has presented with, which can be ruled out by physical examination.

#Major Criteria(all required)

- If the patient presents with an intake of dopamine antagonist, or with dopamine agonist withdrawal within the past 72 hours.
- Hyperthermia
- Severe Muscle Rigidity

#Minor criteria-at least 2 of them should be present

- Diaphoresis i.e(excessive/abnormal sweating without an apparent reason or due to an underlying medical condition)
- Dysphagia
- Tremor
- Incontinence
- Mutism
- Tachycardia i.e (increases heart rate >100 bpm)
- Elevated or labile blood pressure
- Leukocytosis i.e(increases/high WBC count)
- Elevated CK levels
- Altered mental status(10)

There is no significant laboratory test to definitively diagnose NMS, but there are some tests which could support the diagnosis of NMS-

- Creatine Kinase- elevated CK levels may indicate muscle damage in NMS, but it can also be seen in other conditions.
- Comprehensive Metabolic Panel- this includes electrolytes, kidney function tests and other markers to assess overall metabolic status.
- Myoglobinuria- Increased myoglobin in urine can also indicate muscle damage, though it is less common than elevated CK.
- Blood Gas Analysis- this test can reveal metabolic acidosis, which can occur in NMS.
- Other tests like urinalysis, blood cultures, liver function tests, coagulation studies and toxicological screening can be done to rule out any other condition.

Serotonin Syndrome

The diagnosis is primarily based on clinical evaluation which includes a thorough review of symptoms, medical history and current medications of the patient.

These may include Altered mental status, hyperthermia, clonus, hyperreflexia which can be tested by the reflex hammer.

Hunter Serotonin Toxicity Criteria: is often used to aid in the clinical diagnosis of SS. These criteria include:

- ☐ Spontaneous clonus- involuntary rhythmic muscle contractions
- ☐ Agitation or diaphoresis with inducible clonus- Clonus that can be

induced with physical stimulation.

- ☐ Ocular clonus with diaphoresis or agitation: eye clonus
- ☐ Tremor and hyperreflexia- uncontrolled shaking and exaggerated reflexes.
- ☐ Hypertonia, and temperature above 38 degree celsius with ocular clonus.

While there are some nonspecific laboratory findings that may be present, such as increased WBC count. Elevated CPK levels and decreased bicarbonate levels but these are not diagnostic for SS.

Other tests like blood and urinalysis, salicylate and acetaminophen levels, CSF analysis if there is a concern for meningitis or encephalitis can be done.(11)

Treatment

Neuroleptic Malignant Syndrome-

- Stop the antipsychotic drug
- IM/IV Benzodiazepine- lorazepam 1-2mg every i4-6hrs.
- Correct the hypotension and volume loss with intravenous fluids.
- Reduce hyperthermia by cooling blankets, ice packs, antipyretics, and cooled iv fluids.

Rhabdomyolysis can occur as a complication in these patients- maintain hydration and alkalize the urine with IV sodium bicarbonate in these patients to prevent Acute Kidney Injury.

Evaluation and treatment should be carried out in an ICU setting.

- ☐ Bromocriptine can be used if NMS is caused by the withdrawal of antiparkinsonian medication, as it overcomes antipsychotic induced dopaminergic blockade.
- ☐ Amantadine can also be used, it enhances presynaptic release of dopamine and levodopa-carbidopa increases the presynaptic dopamine stores.
- ☐ Dantrolene can be used it inhibits the intracellular calcium release from the sarcoplasmic reticulum to treat muscular rigidity and hyperthermia.(12)
- ☐ Electroconvulsive therapy can be also useful for the treatment of NMS, as it increases dopamine sensitivity and increases dopamine release.(13)

Serotonin Syndrome-

- Stop the medication which caused the syndrome
- In mild to moderate cases
- Give Benzodiazepine- lorazepam, diazepam to decrease agitation and seizure like movements and muscle stiffness in the patients.
- Moderate to severe cases
- Cyproheptadine(Periactin)-is a drug which blocks serotonin production
- Cardiac monitoring
- IV fluids
- Cooling measures

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