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NEUROLEPTIC MALIGNANT SYNDROME: A REVIEW

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Abstract:
Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication associated with the use of neuroleptic drugs. It is a life-threatening neurologic emergency associated with the use of dopamine antagonists, and less commonly with dopamine agonist withdrawal. It occurs with 0.2 % of patients with neuroleptics. First-generation antipsychotic agents are most commonly implicated, but NMS can occur with any antipsychotic agent and also with antiemetic drugs. It presents with the tetrad of clinical features hyperthermia, muscle rigidity, mental status changes, and autonomic dysfunction. Risk factors of NMS include Previous episodes, dehydration, agitation, and the rate and route of neuroleptic administration. Patients with psychiatric illness or mood disorders, especially those on lithium, may be at higher risk for NMS despite the fact that it has been reported in patients with diverse psychiatric diagnoses as well as in normal patients. Important considerations in the differential diagnosis include meningitis, encephalitis, systemic infections, heat stroke, and other drug-induced dysautonomias. The syndrome lasts for 7 to 10 days in uncomplicated cases receiving oral neuroleptics. The treatment mainly consists of early recognition, discontinuation of triggering drugs, management of fluid balance, temperature reduction, and monitoring for complications. Use of dopamine agonists (eg. bromocriptine, amantadine) or dantrolene or both should be considered in treating in more severe, prolonged, or refractory cases. Electroconvulsive therapy (ECT) is an option in patients not responding to drug treatment in the first week, those with residual catatonia persists after other symptoms have resolved, and those in whom lethal catatonia is suspected as an alternative or concomitant disorder. it has been used successfully in the post-NMS patients. As a result of these measures, mortality from NMS has reduced in recent years although fatalities still occur. In the majority of patients who have recovered from an NMS episode, neuroleptics may be safely reintroduced. The lack of knowledge regarding NMS may delay the onset of therapy, impair the quality of treatment, and lead to a worse outcome or even cause death.

KEYWORDS: *Neuroleptic Malignant Syndrome, Dopamine antagonist, Hyperthermia, Dantrolene, Electroconvulsive therapy*

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INTRODUCTION:

Neuroleptic Malignant syndrome (NMS) is a rare, but potentially life threatening neuropsychiatric condition which arises as a side effect that can occur in response to treatment with Antipsychotic drugs. [1,2] NMS is considered as a Neurologic emergency characterized by a tetrad of distinctive clinical features fever, rigidity, mental status changes, and autonomic instability along with elevated serum creatinine phosphokinase and white blood cells count. [3]

Muscle rigidity that is unresponsive to Anticholinergic therapy may be the first sign of NMS and it is simultaneously associated with fever. Rigidity may range from muscle hypertonicity to severe "lead-pipe rigidity". Parkinsonian findings are common in NMS and other movement disorders present at the same time like tremors, abnormal reflexes, bradykinesia, chorea, dystonias, nystagmus and opsoclonus, dysphagia, dysarthria, aphonia and seizures. [3,4] NMS has been reported among patients of all ages but more in men than women. [1] Patients with suspected NMS usually have a history of Neuroleptic or Antipsychotic therapy. Newer atypical antipychotics clozapine, risperidone, and olanzapine are capable of inducing the syndrome. [10,11] Although in many of these cases questions remain about the impact of concommitant diseases and medications. The anti-emetic metoclopramide and the tricyclic antidepressant amoxapine have also been a cause to NMS because of their dopamine blocking actions. complications of NMS include psychologic consequences of severe rigidity and immobilization and other serious complications such as myocardial infarction, disseminated intravascular coagulation and sepsis. [20]

EPIDEMIOLOGY

In 1956, The first reported case of NMS was appeared, shortly after the introduction of the antipsychotic drug chlorpromazine (thorazine). [1] A severe illness known as neuroleptic malignant syndrome (NMS) is caused on by a negative response to drugs with dopamine receptor antagonist effects or by the abrupt discontinuation of dopaminergic medicines. [8] In 1960, French clinicians reported on the adverse effects of the newly introduced neuroleptic haloperidol and described a "syndrome malin des neuroleptiques," giving the syndrome its current name. [2,6] Pooled data from 1966 to 1997 suggested the incidence of NMS ranges from 0.2% to 2%. Although young adults make up the majority of NMS patients, the syndrome has been reported in people of all ages, ranging from 0.9 to 78 years. [3,5,7] Both factors such as age and sex corresponds with the distribution of the exposure to antipsychotic agents. [5,8]

CLINICAL PRESENTATIONS

Patients usually experience NMS within hours or days of being exposed to a substance that causes it, with the majority showing symptoms within two weeks and almost all within a month. NMS has traditionally been defined by the tetrad of fever, muscle rigidity, and altered mental status and autonomic dysfunction. [10] These symptoms develops over the course of one to three days. Every characteristic is found in 97 to 100% of cases.

In 82% of cases Mental status change is reported as initial symptom which includes agitation or delirium. Mutism and catatonic signs may be apparent. The normal progression is to profound encephalopathy with stupor and eventually coma.

Muscular rigidity is widespread and often extreme. The increased tone is characterised by "lead-pipe rigidity," or stable resistance through all ranges of motion, and can be experienced while moving the extremities. Superimposed tremor may result in a ratcheting quality or a cogwheel phenomenon. Other motor anomalies include tremor (seen in 45 to 92 percent), dystonia, opisthotonus, trismus, chorea, and other dyskinesias. [3,5] Additionally, patients may experience severe sialorrhea, dysarthria, and dysphagia. [12]

According to many diagnostic standards, hyperthermia is a defining symptom. Temperatures higher than 38°C are typical and even high temperatures more than 40°C are common. Patients with NMS associated with second-generation antipsychotic drugs may experience fever less frequently. [41,42]
Tachycardia (in 88%), hypotension or high blood pressure (in 61–77%), and tachypnea (in 73%) are the three main manifestations of autonomic instability [3,22]. Dysarrhythmias could happen, Intense diaphoresis is common. [18]

Laboratory abnormalities

Elevated serum creatinine kinase (CK) – laboratory findings often reflect the clinical manifestations of NMS, with profound elevation off creatinine elevation due to severe rigidity.[31] In NMS, CK level often exceeds 1000 international units per litre and occasionally reaches a value of 100,000 international units per litre. If rigidity is not clearly well developed, particularly at the outset of the condition, normal CK can be observed.

Elevated CK, especially in the mild to moderate range, is not always associated with NMS but it is frequently

observed individuals with acute and chronic psychosis due to intramuscular injections and physical constraints.[27] However, CK levels above 1000 IU/L are likely more specific for NMS, and the degree of CK elevation corresponds with the severity and prognosis of the disorder [24]. Other laboratory findings are common but nonspecific to NMS. A consistent laboratory finding is leukocytosis, with a white blood cell count ranges from 10,000 to 40,000/mm3 [5,22]. Mild elevation in liver transaminases, alkaline phosphatase and lactate dehydrogenase are common. Electrolyte abnormalities such as hypocalcemia, hypomagnesemia, hypo- and hypernatremia, hyperkalemia, and metabolic acidosis are frequently observed. The rare symptom Rhabdomyolysis may lead to myoglobinuric acute renal failure [45]. Low serum iron levels are frequently observed in NMS patients (mean 5.71 micromol/L; normal 11 to 32 micromol/L) and are a sensitive but nonspecific marker of NMS in acutely ill psychiatric patients [40].

PATHOPHYSIOLOGY

The most widely acknowledged mechanism by which antipsychotics causes neuroleptic malignant syndrome is that of dopamine D2 receptor antagonism. Current theories are constrained in their ability to explain all clinical manifestations and in supporting data. An animal model for NMS has been designed, but it does not fully correspond with the human syndrome. [31,32] Because of the class of drugs with which NMS is associated, dopamine receptor blockade is core to most theories of its pathogenesis.

In this model, central D2 receptor blockade in the hypothalamus may cause hyperthermia and other signs of dysautonomia. [33,34] Interference with nigrostriatal pathways, and spinal cord leads to increased muscle rigidity and tremor via extrapyramidal pathways. Peripherally, antipsychotics stimulate the sarcoplasmic reticulum to release more calcium, which increases contractility and can cause hyperthermia, rigidity, and muscular cell damage. This represent a primary skeletal muscle defect or a direct toxic effect by these drugs on skeletal muscle.[15]

Beyond these direct effects, D2 receptor blockade might cause NMS by reducing the sympathetic nervous system's tonic inhibition. The resultant sympathoadrenal hyperactivity and dysregulation leads to autonomic dysfunction. [35]

A genetic mechanism underlying this process has been studied as familial clusters of NMS. Genetic studies have shown that the presence of a specific A1 allele of the dopamine D2 receptor (*DRD2*) gene is over-represented in NMS patients that has been associated with low density and function of dopamine D2 receptors in the brain, mostly on the corpus striatum on the caudate region. Carriers of the A1 allele have a 10.5 times increased risk of developing NMS than noncarriers. [13]

Some other neurotransmitter systems gamma aminobutyric acid, epinephrine, serotonin, and acetylcholine also appear to be involved, either directly or indirectly [31,35].

RISK FACTORS

Every class of antipsychotics has been associated with NMS, including low-potency neuroleptics (eg,chlorpromazine), high-potency neuroleptics, and the newer or atypical (eg, clozapine, risperidone, olanzapine) antipsychotics as well as antiemetic drugs (eg, metoclopramide, promethazine, and levosulpiride). [5,12,13] where as it is most oftenly seen with high potency first generation antipsychotic agents, formerly called neuroleptic agents (eg, haloperidol, fluphenazine)[9,11]. Lithium at toxic levels may also reportedly cause NMS. [14]

The clearest risk factors for NMS depends on the time course of therapy.

Associated factors- High-potency neuroleptic use, High-dose neuroleptic use, Rapid increase in neuroleptic dose, Depot injectable (long-acting) neuroleptic use (ie., fluphenazine decanoate, fluphenazine enanthate, haloperidol decanoate, risperdal consta), initial episodes of neuroleptic malignant syndrome, Recent episode of catatonia, comorbid substance abuse or neurologic disease, and acute medical illness (including trauma, surgery, and infection). [16]

Other potential risk factors- Dehydration, Agitation [17], Exhaustion, Malnutrition, Organic brain syndromes, Non schizophrenic mental illness, Past history of electroconvulsive therapy, Warm and humid environments, Inconsistent use of neuroleptics, Postpartum period [18]

Genetic factors might also play a role. Case reports have been published on NMS occurring in identical twins as well as in a mother and two of her daughters. [19]

A number of demographic characteristics have been implicated, including male sex (2:1 ratio) and age 20-25 years.

Although symptoms usually appear during the first two weeks of antipsychotic therapy, the association of the syndrome with drug use is idiosyncratic. NMS can develop after a single dose or years of treatment with the same medication at the same dose, the phenomenon is not dose-dependent, but higher doses are a risk factor. [5] Recent or rapid dose escalation, switching from one medication to another, and parenteral administration are reported as risk factors in case control studies. [15,16]

In patients who have experienced an episode of NMS, the risk of recurrence is strongly related to the length of time between the episode and resumption of antipsychotics. [20] Delaying reintroduction of antipsychotic medication until at least 2 weeks after the symptoms gets subsided and is typically recommended for patients who had been taking an oral antipsychotic and at least 6 weeks for those on a depot form. The chances of recurrence may be reduced by switching to a different antipsychotic class of drug and, if possible, using an atypical antipsychotic rather than a traditional agent. [48]

DIAGNOSIS

The diagnosis of NMS is made in a patient who is taking an associated medication and who exhibits a typical clinical condition. Although there is no diagnostic test for NMS, testing plays a crucial role in the diagnosis of patients with potential NMS. Typical laboratory abnormalities support the clinical diagnosis, while other conditions are ruled out and patients are followed for NMS consequences using other tests. [32]

Brain imaging tests and lumbar punctures are necessary in patients who may have NMS in order to rule out structural brain illness and infection. [47] Computed tomography (CT) and magnetic resonance imaging (MRI) are usually normal.

There have been a few isolated cases of diffuse cerebral edema in association with severe metabolic disturbances [30], as well as cerebellar and basal ganglia signal abnormalities resembling malignant hyperthermia (MH). [31] Although cerebrospinal fluid is often normal, a non-specific protein elevation has been observed in 37% of cases.

In order to rule out nonconvulsive status epilepticus, electroencephalography may be performed. Generalized slow wave activity is observed in NMS patients.

DIFFERENTIAL DIAGNOSIS

Two major categories can be used to characterise the differential diagnosis of NMS: those conditions that are related to NMS and those that are unrelated to NMS but frequently taken \
into consideration. NMS is one of a group of acute dysautonomias that includes features such as rigidity, hyperpyrexia, and dysautonomia [37,42].

Serotonin syndrome

Serotonin syndrome is the most commonly diagnosed related condition to NMS [43,44]. This typically results from the use of selective serotonin reuptake inhibitors and has a similar clinical presentation that makes difficult to distinguish from NMS. Shivering, hyperreflexia, myoclonus, and ataxia are common signs in these patients that are uncommon in NMS patients [35]. Nausea, vomiting, and diarrhea are also a common part of the prodrome in serotonin syndrome and are rarely reported in NMS. Rigidity and fever when present, are less severe than in patients with NMS. Although the symptoms of serotonin syndrome often progress more quickly than those of NMS, the onset time of the two disorders can vary and overlapping [37].

Malignant hyperthermia

Malignant hyperthermia (MH), a rare hereditary condition, can be separated from NMS in the clinical setting as it occurs after administration of halogenated inhalational anaesthetics (eg, halothane) or depolarizing muscle relaxants (eg, succinylcholine) to genetically susceptible individuals. When one of the aforementioned medications is given to skeletal muscle, an excessive amount of calcium is released from the sarcoplasmic reticulum as a result of an underlying defect caused due to autosomal dominant mutation in the ryanodine receptor.

However, MH has also been documented in patients with MH susceptibility who are exposed to heat stress or vigorous exercise. Its clinical presentation with hyperthermia, muscle rigidity, and dysautonomia is quite similar to NMS, although often more fulminant. [18]

Malignant catatonia

The most difficult condition to distinguish from NMS in terms of differential diagnosis, it exhibits rigidity and heat. However, there is typically a behavioural prodrome in this disease that lasts for a few weeks and is marked by psychosis, agitation, and catatonic excitation. Additionally, the motor symptoms are more positive phenomena than NMS describes them in terms of dystonic posture, waxy flexibility, and stereotyped repetitive movements. [19]

TREATMENT AND MANAGEMENT

The management of patients with NMS should be based upon clinical severity and diagnostic certainty. When symptoms are severe, monitoring and treatment in an intensive care unit are needed.

Supportive care — The need for immediate and aggressive supportive care in NMS is essential and uncontroversial [41]. Admission to the intensive care unit is necessary due to the intensive nature of the necessary monitoring and supportive care.

Pharmacological treatment is often successfully used in patients with moderate or severe clinical manifestations of NMS. Commonly used agents are dantrolene, bromocriptine, and amantadine.[46]

A reasonable approach is made to start with benzodiazepines (lorazepam or diazepam) along with dantrolene in cases with moderate to severe muscle rigidity with elevated CK; bromocriptine or amantadine can also be added for patients with moderate to severe illness [38].

Benzodiazepines - Lorazepam is used 1 to 2 mg IM or IV every four to six hours. Diazepam is given as 10 mg IV every eight hours.

Benzodiazepines, particularly diazepam, may also have a muscle-relaxing effect in addition to mitigating agitation. [37]

Dantrolene is a direct-acting skeletal muscle relaxant and is an excellent treatment for malignant hyperthermia (MH). Adults commonly get doses of 1 to 2.5 mg/kg IV, which can be repeated up to a daily dose of 10 mg/kg [40]. Effectiveness includes a decrease in heat production as well as rigidity, and the results are observed within minutes of administration. Dantrolene is associated with the risk of hepatotoxicity, and it should be avoided if liver function tests are extremely abnormal. While some recommend stopping it after a few days, others advise continuing for 10 to 14 days, then slowly tapering off to reduce the risk of relapse.

Bromocriptine, a dopamine agonist, is prescribed to recover the lost dopaminergic tone. [38] In psychotic patients it is well tolerated. Doses of 2.5 mg (through nasogastric tube) every six to eight hours are titrated up to a maximum daily dose of 40 mg. it is continued for 7 to 14 days after NMS is controlled and then slowly tapered.

Amantadine is used as an alternative to bromocriptine has dopaminergic and anticholinergic effects. An initial dose is 100 mg orally or via gastric tube and is titrated as needed to a maximum dose of 200 mg every 12 hours. [46]

Other medications used in the treatment of NMS include levodopa (especially in individuals with NMS associated with antiparkinson drug withdrawal) [25,34] apomorphine, carbamazepine, bupropion, and dexmedetomidine. [34]

Electroconvulsive therapy (ECT) is often only used for patients who have failed other therapies or who require non-pharmacological psychiatric treatment. The use of ECT is rationale inn NMS treatment as its efficacy in treating malignant catatonia and reports of parkinsonism improving with ECT. There are safety concerns about ECT in NMS. Cardiovascular complications occurred in 4 of 55 patients, including 2 patients with ventricular fibrillation and cardiac arrest with permanent anoxic brain injury. [30] Some other patients had status epilepticus. Aspiration pneumonia and uncontrolled spontaneous seizures been reported as complications of ECT for NMS by other writers as well. [39]

PROGNOSIS

Most NMS cases resolve within 2 weeks. Mean recovery time reported are 7 to 11 days. Cases persisting for six months with residual catatonia and motor signs are reported. [6] Depot antipsychotic usage and concurrent structural brain illness are risk factors for a prolonged course. [22] Most patients recover without neurologic consequences except where there is severe hypoxia or grossly elevated temperatures for a long duration. 5 to 20 percent mortality rates reported for NMS are the strongest predictors of mortality rate are disease severity and the occurrence of medical complications. [47]

CONCLUSION:

The optimal treatment of this potentially life-threatening syndrome is not assured yet, and current guidelines do not represent an adequate help offering a practicable therapy concept with a high evidence level. Benzodiazepines, dantrolene, bromocriptine, and amantadine have significant benefits. ECT is an effective therapeutic alternative in case of treatment failure. The lack of knowledge regarding NMS can delay the initiation of therapy, impair the quality of treatment, and ultimately lead to a worse outcome or death. To improve the clinical outcome a thorough revision of the current treatment guidelines is essential.

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