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Case Report

Neuroleptic malignant syndrome: case report

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is an infrequent, but potentially life-threatening neurologic emergency associated with the use of neuroleptic or antipsychotic drugs. A 43 years old male with a history of trigeminal neuralgia developed Neuroleptic malignant syndrome while receiving Carbamazepine and Amitryptylline. Treatment is mainly supportive and includes withdrawal of the neuroleptic medication and, possibly, administration of drugs such as dantrolene and bromocriptine. Complications of NMS include acute renal failure and acute respiratory failure. The possible etiologies, triggering factors and treatment are discussed with reference to existing literature.

Keywords: Neuroleptic malignant syndrome, Dopamine receptor, Creatinine kinase, Hyperpyrexia, Sarcoplasmic reticulum

INTRODUCTION

Neuroleptic malignant syndrome may be a rare but life-threatening, idiosyncratic reaction to neuroleptic/antipsychotic medication. It is characterized by fever, muscular rigidity, altered mental status, autonomic dysfunction and elevated creatine phosphokinase.[1] It was first described by Delay and colleagues in 1960, shortly after the introduction of antipsychotic medications to psychiatry.[2] Incidence rates for NMS ranges from 0.02% to 3% among patients taking neuroleptic drugs and its diagnosis represents a significant challenge for clinicians.[3] Here, we report the occurrence of NMS in a patient who received a combination of carbamazepine and amitriptyline.

CASE REPORT

A 43-year-old male with a history of trigeminal neuralgia (on tablet Carbazepine 200 mg BD and tablet Amitryptylline 10 mg HS from August 2018) was admitted in our hospital for workup for a prior suspected MSSA bacteremia. Prior to the admission, patient was admitted elsewhere with high grade fever with chills and rigors, cough with yellowish expectoration and loss of weight and had been diagnosed with suspected MSSA bacteremia with infective endocarditis. He was treated with injection Cefazolin 2 gm and developed loose stools and skin rashes. After admission to our hospital, injection Daptomycin 350 mg was given STAT for MRSA infection due to suspected drug reaction to cephalosporin. His vital signs showed temperature: 98.6°F, pulse rate: 110 beats/minute, blood pressure: 110/70 mm of Hg and respiratory rate: 22/minute. Soon after admission, the patient developed hyperpyrexia associated with restlessness, anxiety and muscle rigidity and increased work of breathing. His temperature shooted upto 108°F, HR 178 / min, RR 30/min and BP became 110/50 mmHg, he was shifted to ICU and intubated in view of respiratory distress. The patient received IV paracetamol and antipyretic measures like iv normal saline 1 L, injection Calcium gluconate, 25% dextrose 50 ml and injection Sodium bicarbonate, cold pack etc and temperature was decreased to 102◦F. injection Diazepam 10 mg STAT was given. Injection

Flucloxacillin was started. On the first day of admission, a battery of tests was requested, and the results were as follows: CPK level was 1304 U/L with serum procalcitonin 26.33 ng/ml, GGTP 452 U/L, ALP 162 U/L and normal Hb and WBC. Arterial blood gases level showed increased Lactate levels (3.91). Liver function tests, PT, PTT, INR, lipid profile, urine analysis, ESR, ECG, Echo, CXR and culture sensitivity tests were all normal. The neurologist was consulted and a diagnosis of NMS was made. Amitryptylline, and Carbamazepine was stopped and tablet Bromocriptine 5 mg was started every 8 hours.

Table 1

A.	**Development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.**
B.	Two (or more) of the following:
	Diaphoresis
	Dysphagia
	Tremor
	Incontinence
	Changes in level of consciousness ranging from confusion to coma
	Mutism
	Tachycardia
	Elevated or labile blood pressure
	Leukocytosis
	Laboratory evidence of muscle injury (example: elevated CPK)
C.	The symptoms in criteria A and B are not due to another substance or a neurological or other general medical condition.
D.	The symptoms in criteria A and B are not better accounted for by a mental disorder.

On second day, the patient continued to have fever (temperature: 101 F), CPK levels decreased to 1112 U/L, lactate level was 1.10. injection Paracetamol 1 gm IV was given. On third day, the patient had fever spikes, lactate levels decreased to 1.02 and was extubated but had difficulty in swallowing with pain. Shifted to ward, gradually the signs and symptoms of patient improved and all medications were tapered off. After one week of hospital stay patient's condition improved remarkably and was discharged.

DISCUSSION

A case presentation of neuroleptic malignant syndrome in a young, male patient with known trigeminal neuralgia and treated with Amitryptylline and Carbamazepine is reported.

According to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition [DSM-IV]) Research Criteria for Neuroleptic Malignant Syndrome (Table 1).[20]

Exposure to dopamine blocking agents, severe muscle rigidity and fever and minor criteria:

CPK >4-timesthe upper limit, Changes in mental status (delirium, altered consciousness), Autonomic activation, including: tachycardia (>25% above baseline), diaphoresis, blood pressure elevation (systolic or diastolic 25 mmHg over baseline), or fluctuation (20 mmHg diastolic change or 25 mmHg systolic change).

Our patient presented all of the major criteria, and six of the minor criteria (raised CK, tachycardia, fluctuated blood pressure, altered consciousness and dysphagia). While the patient clearly displayed the classic features suggestive of NMS, there are several atypical aspects of the case worthy of discussion. The incidence of NMS is about 1% in patients treated with antipsychotic medications. NMS has been reported in all age groups, in cold climates and throughout the seasons in parallel with the use of neuroleptics.[3,4] Because this is still a high mortality rate, it is important for clinicians to watch for early signs and symptoms of NMS. Although NMS is often regarded in the literature as an idiosyncratic and unpredictable reaction related to the administration of dopamine antagonists and other compounds, there are a number of risk factors that increase the likelihood of developing NMS. These risk factors can be grouped into four categories, which include pharmacological risk factors (type of drug, pharmacokinetics, polypharmacy) environmental (high ambient temperature, restraint, dehydration); demographic (age, concurrent medical conditions or co morbidity); and genetic liability (history of previous NMS, family history of catatonic disorder, channelopathy). Although NMS can occur any time during the course of drug treatment, it occurs more frequently during either the initial months of treatment or after a dosage change. In this regard, higher doses of antipsychotic drugs are correlated with a greater risk of developing NMS. In addition, parenteral routes of administration, either intramuscular or intravenous, have also been associated with greater risk. NMS is a life-threatening iatrogenic neurologic emergency, manifested as a characteristic clinical syndrome and likely results from a complex interaction between the neuroleptic medication and a susceptible host. Two theories are proposed to elucidate the syndrome: central dopamine receptor blockade and striated muscle defect. In the first theory, the dopaminergic receptor antagonism by neuroleptics may interfere with dopamine's normal role in central thermoregulation. Heat is produced from serotonin stimulation in the hypothalamus, and dopamine inhibits this process. Dopaminergic blockade therefore results in less inhibition of serotonin stimulation and contributes to the hyperthermia seen in NMS. it is unlikely that the syndrome is thanks to central dopaminergic blockade alone.[6-8] Furthermore, dopamine may directly inhibit striated muscle contraction, and thus dopamine blockade may end in increased skeletal muscle contraction.[5] On a clinical basis, the diagnosis is settled when four features of the syndrome are fulfilled: change of mental status,

rigidity, hyperpyrexia, vegetative deregulation of the autonomic systema nervosum (including blood pressure fluctuations). When any two of those above-mentioned features appear, diagnosis should be suspected within the setting of psychotropic drug therapy (when treating psychosis) or dopamine withdrawal (in cases of Parkinsonism). Withdrawal of therapy with intrathecal baclofen has, also in several cases, been related to an NMS-like syndrome. The difference here is that increased muscular tone is of a rebound spastic-type instead of being a rigid one, otherwise the spectrum of symptoms appears quite just like those of NMS. Clinicians need to take into consideration that the importance of medical diagnosis, including meningitis, encephalitis, septic shock (systemic infections), heat stroke, and other iatrogenic dysautonomias. Concerning the results from laboratory investigations, these should assist in ruling out the likelihood of the above-mentioned tentative diagnoses, especially the elevated CK values. An elevated level of this enzyme is a common observation in NMS although it is not a pathognomonic finding in the syndrome. The approach to a case of NMS, and its general management, should be supported a hierarchy of the severity of clinical features and thus enable the right diagnosis to be made. Taken together, when there is any possible suggestion of NMS, the administration of psychotropics should be stopped, and the patient should be admitted for close observation to evaluate the clinical signs and to perform the relevant laboratory investigations. This should be wiped out an ICU, especially for patients who have significant hyperpyrexia and rigidity. This is because these individuals need aggressive supportive care. One should evaluate biological treatment with dantrolene, bromocriptine, and/or amantadine in patients who have significantly elevated CK values or hyperpyrexia on the primary presentation, and in those that are irresponsive to withdrawal of a psychotropic drug (or the offending drug) within the primary 48 hours of admission. Patients who don't answer medical therapy during the primary 7 days, especially those with persistent catatonia after the resolution of other symptoms, lethal catatonia should be regarded as an alternate diagnosis or as a concomitant sequel, then ECT should be seriously considered. The patient has got to be advised to drink sufficient amounts of liquids (water and alcohol-free beverages) to stay the body hydrated, to regulate blood heat, and to make sure proper kidney function. Environmental therapy features a vital role here, since patients should be under observation with reference to their fluid intake even when the patient is on an atypical antipsychotic therapy regime. Over hydration (water intoxication) has also been blamed for causing NMS, so a balanced water intake may be a pivotal factor for both optimal metabolism and therefore the pharmacology of the antipsychotic agent(s) the patient is using, and to take care of normal renal function. The patients themselves should be orientated and alerted about the first symptoms of possible relapse, and that they should be called in to a psychiatric outpatient institution for a periodic checkup and clinical observation. One of the problems causing an excellent dilemma in NMS is that the hyperpyrexia, where there's no convincing explanation for its pathophysiology.

Treatment

For treatment, it's essential to acknowledge the symptoms and to prevent the neuroleptic therapy immediately. Supportive therapy, like fever reduction, hydration and nutrition, is vital until the blood levels of the major tranquilizer decrease. it's controversial whether specific therapies are beneficial additionally to the supportive therapy. The role of intravenous dantrolene sodium therapy, used widely in autosomal dominant disease, is unclear, but it's still administered to scale back blood heat and to relax peripheral muscles by inhibiting the discharge of calcium from the sarcoplasmic reticulum of muscle.[1] The recommended dose is 2 mg/kg intravenously, repeated every 10 minutes if necessary, to a maximum of 10 mg/kg daily it's only usually given within the acute stage and not continued for quite a couple of days.[1] Hepatotoxic effects may occur if the daily dose exceeds 10 mg/kg. Bromocriptine, a dopamine agonist, usually improves muscle rigidity within a couple of hours, followed by a discount in temperature and an improvement in vital sign. Bromocriptine is given to reverse the hypo dopaminergic state and is administered orally (or via nasogastric tube), starting with 2.5 mg 2 or 3 times daily and increasing doses by 2.5 mg every 24 hours until a response or until reaching a maximum dose of 45 mg/d.[16-19] Dantrolene can be administered intravenously starting with an initial bolus dose of 1 to 2.5 mg/kg followed by 1 mg/kg every 6 hours up to a maximum dose of 10 mg/kg/d.[16-19] Oral dantrolene is used in less severe cases or to taper down from the intravenous form after a few days with doses that range from 50 to 200 mg/d. Due to a risk of hepatoxicity, dantrolene is typically discontinued once symptoms begin to resolve. Bromocriptine, however, is generally maintained for at least 10 days for NMS related to oral neuroleptics and 2 to 3 weeks for depot neuroleptics1. Doses of two 0.5–10 mg up to 4 times daily are used with some success.[9] Hypotension is that the commonest adverse effect of bromocriptine therapy. It are often mild or severe, and treatment would be almost like that of other causes of hypotension. it's unknown what affects the degree of hypotension and other autonomic factors. Dantrolene and bromocriptine could also be used together, without more adverse effects than with either one alone.[13] Amantadine and levadopa–carbidopa are used successfully to scale back hyperthermia in patients with NMS.[14] Treatment of NMS must be continued for 2–3 weeks until symptoms remit. due to possible exacerbation of NMS symptoms, dopamine antagonists like metoclopramide should be avoided.

CONCLUSION

As the majority of NMS cases are attributed to the utilization of antipsychotic agents, especially first-generation (conventional or typical) drugs, one should take care when prescribing such agents to psychotic patients.

The present trend in many psychiatric centers of the developed world is that the use of second-generation (atypical) agents. In other words, the syndrome can still be encountered even with the supply of the second-generation of newly designed agents, although the clinical picture could be milder than what's encountered in NMS with typical antipsychotics it's also necessary to say here that the utilization of medicine aside from antipsychotic agents can cause NMS, for instance, drugs like metoclopramide (antiemetic), amoxapine (tetracyclic antidepressant), halopidridol (typical antipschychotic) amitriptilline (tricyclic antidepressant), carbamezapine (tricyclic antidepressant) and lithium (mood stabilizer) are recognized as being perpetrators of NMS and careful periodic clinical observation of psychotic patients is warranted, especially those that have recently started taking antipsychotics. This action may help the first diagnosis of NMS and thus ensure an early start of treatment intervention with the hope of minimum negative consequences. It's clear that the bulk of medicine that are related to the induction of NMS are either antipsychotics or antidepressants. These groups of medicine are cornerstones as biological treatment tools in contemporary clinical psychiatry. it's evident that these drugs haven't any selective actions when prescribed as monotherapy and therefore the optimal therapy may require polypharmacy, a incontrovertible fact that increases the spectrum of anticipated side effects, including NMS.

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