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Neuroleptic Malignant Syndrome with Very High Serum Creatine Phosphokinase: A Case Report

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Abstract

The neuroleptic malignant syndrome (NMS), characterized by muscular rigidity, altered level of consciousness, dysautonomias and an elevated creatinine phosphokinase level, is a potentially lethal consequence of treatment with neuroleptics. Although it occurs most frequently with conventional anti psychotics, it may also occur with newer anti psychotic agents. Physicians need to have a high index of suspicion with regard to diagnosing NMS in patients taking neuroleptics regardless of duration or dose and presenting with hyperthermia. It is under diagnosed in critical care settings though various neuroleptics are frequently used in intensive care units for various purpose. We report a case involving a 55-yr old man with psychiatric disorder who presented with NMS with extremely elevated serum creatine phosphokinase level and acute renal failure.

Key words: *Neuroleptic malignant syndrome; Acute renal failure; Anti psychotic drugs.*

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Introduction

The neuroleptic malignant syndrome is a rare, potentially life threatening condition resulting from the use of neuroleptic medications, and other agents which are dopamine blocking or depleting. It may also result from rapid withdrawal of dopamine agonists (e.g. levodopa-carbidopa, amantadine). It presents as a myriad of signs and symptoms with varying degrees of severity. Diagnosis of NMS warrants immediate attention. Treatment consists of rapid discontinuation of the offending agent and clinical management of the patient.

Case Report

A 55-year old diabetic & hypertensive gentleman, working in forest dept in hilly areas of Chittagong, was admitted in an ICU (outside BIRDEM) with complaints of high grade intermittent fever & irrelevant talks for 1 week followed by loss of consciousness. His medical history revealed multi infarct dementia with occasional aggressive behavior for last 2 years. Medications prescribed by different private neurologists for the preceding 6 months included olanzapine, haloperidol, clozapine, quetiapine, rivastigmine & donepezil given in combination on different occasions.

On admission he was provisionally diagnosed as a case of Meningoencephalitis (CSF protein 87 mg/dl, TWBC 20/cmm, L 80%, N 20%), & was treated with I/V antibiotics & antiviral (aciclovir). He was placed on MV support for type I respiratory failure. Initial investigations revealed TWBC 14 x 10^6/iL with 86% neutrophils, platelet 51 x 10^3/iL, SGOT 140U/L, SGPT 71U/L, & CPK 1072U/L. Tracheal aspirates, urine & paired blood cultures were negative for bacterial growth. Anti Dengue IgG & IgM antibodies and ICT for malaria were negative. CT scan of head showed cortical atrophy with right paraventricular lacunar infarction. His initial urea was 33 mg/dl & creatinine was 1.1mg/dl, which increased to 241 mg/dl & 6.3 mg/dl respectively in 5days. So, renal replacement therapy was advised and patient was transferred to ICU of BIRDEM hospital.

On admission at ICU, BIRDEM, patient was unconscious grade IV, had temperature 102°F (rectally) & was placed on MV. His pulse was 108/min & BP was 140/70mmHg. No skin rash was observed, & liver,

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Table-I

*Neuroleptic medications associated with NMS**

Typical neuroleptics:		Atypical neuroleptics:	
Haloperidol †	+++	Clozapine †	+
Chlorpromazine	++	Olanzapine †	+
Fluphenazine	++	Quetiapine†	+
Levomepromazine	+		
Loxapine	+	Risperidone	+

*+, ++, +++ = frequency of association with NMS
†= drugs which our patient received prior to admission

spleen, kidneys & lymph nodes were not enlarged. There were features of consolidation in right lower chest on clinical examination & it was supported by chest x-ray. He had generalized rigidity involving limbs & neck. Deep tendon reflexes could not be elicited properly due to rigidity & plantar responses were equivocal. His temperature fluctuated from 101°F to 107°F (rectally). ABG showed P^H 7.20, PO_2 87mmHg, PCO_2 34mmHg, HCO_3^- 13.3mmol/L, base deficit 13.7, SaO_2 94% on FiO_2 0.50. Serum K^+ was 7.5mmol/L, urea 385mg/dl & creatinine 9.8mg/dl. Urine dipstix was positive for blood; but there was no red cell on microscopic examination. His CPK was 2 49 100 U/L with CK-MB-2013 U/L. ECG was within normal limit. Repeat CSF study showed protein 70mg/dl with TWBC 14/cmm (100% lymphocytes).

A diagnosis of Neuroleptic Malignant Syndrome along with Pneumonia & Acute Renal Failure was made. Hemodialysis was started soon after admission. Antibiotics were given according to culture-sensitivity report. 4 days after admission, treatment with Bromocriptine & Levodopa-carbidopa was started with gradual increment of dose of Bromocriptine. His temperature came down to 101°F (rectally) within a week with significant improvement of generalized muscular rigidity. Repeat CPK levels fell to 86336, 38980, 41500, 418, & 161 U/L on day 6, 9, 12, 17 & 22 respectively. Bromocriptine was tapered off. Patient had spontaneous eye opening 20days after admission but was still non-responsive. Elective tracheostomy was done.

On day 26, his attendants refused to continue hemodialysis and subsequently refused MV support because of financial reason. They also signed a DNR (do not resuscitate) request. Consequently patient died in next few days.

Table-II

Complications associated with NMS

Rhabdomyolysis †	Seizure
Renal failure †	Sepsis †
Pulmonary embolism	Myocardial infarction
Aspiration pneumonia †	Hepatic failure
Escherichia coli fasciitis	DIC

†= complications associated with our patient.

Discussion

NMS is an idiosyncratic, life-threatening complication of treatment with antipsychotic drugs that is characterized by fever, severe muscle rigidity, and autonomic and mental status changes. The incidence is estimated to range from 0.02-2.4% with conventional antipsychotics and a much lower incidence for atypical antipsychotics.[1] The mortality is between 10% and 70%.[2]

NMS is a hypodopaminergic state of the brain. Neuroleptics cause dopamine receptor blockade at the striatum and hypothalamus. There may also be a hypernoradrenergic state in NMS, accounting for cardiovascular instability.

All ages and both sexes are affected in the NMS, but males are affected twice as often as females.[3] NMS typically develops over a period of 24-72 hr. The risk of developing NMS has been reported to last for 10-20 days after discontinuation of oral neuroleptics. Virtually all neuroleptics are capable of inducing the syndrome; including the newer atypical antipsychotics (Table 1).[4] Our case had history of taking olanzapine, haloperidol, clozapine and quetiapine of unknown doses within 6 months of developing NMS. Dehydration, stress, humidity, sudden withdrawal of L-dopa or dopamine agonists in patients of Parkinson's disease, concomitant use of lithium, anticholinergics, or some antidepressants, and sudden dose reduction or change of antipsychotics have been implicated as risk factors for NMS.[5] Though there was no history of sudden change of neuroleptic drugs or dosage in our case prior to admission, he had history of Meningoencephalitis diagnosed 5 days prior to admission in our ICU, which acted as a risk factor.

Many diagnostic criteria have been proposed for NMS but no single set of criteria is used universally. Presence of hyperthermia, rigidity and elevated CPK

concentration indicate a high probability of NMS. Rigidity and akinesia develop concomitantly with, or shortly before, temperature elevations as high as 106°F. Consciousness fluctuates from an alert but dazed mutism through stupor and coma. Dysarthria, dyskinesias and features of parkinsonism are associated extra pyramidal symptoms. Involvement of the autonomic system is manifested by severe tachycardia, labile blood pressure, profuse diaphoresis and urinary incontinence. Decreased chest wall compliance resulting from generalized muscle rigidity leads to tachypnoeic hypoventilation and pulmonary infection secondarily. Our patient met the major criteria of diagnosis e.g. rigidity, fever and elevated CPK although pneumonia was also a cause for rise of temperature.

Several laboratory abnormalities are associated with NMS, although none are pathognomonic of diagnosis. These are essential to exclude other diseases or complications. The CPK level is always elevated reflecting myonecrosis, with the risk of subsequent myoglobinuric renal failure. Serum aldolase, transaminases, and lactic acid dehydrogenase concentrations are also increased significantly. Patients may have metabolic acidosis, hypoxia, elevated serum catecholamines, and leukocytosis. CSF analysis is normal in more than 95% of cases. Neuroimaging findings are generally within normal limits. Our patient had unusually high level of CPK (249000 U/L). CPK level is usually range from 500-3000 U/L in most of the reported cases.[6] Highest reported rise of CPK was 61153 U/L recorded in the most recent literatures.[7] So, our patient had the highest CPK level among cases so far reported. He developed acute renal failure requiring hemodialysis. Presence of myoglobinuria could not be tested because of lack of facility. But there was moderate elevation of SGPT (327 U/L) and significant rise of LDH (11260 U/L).

Differential diagnosis is of prime importance because NMS is a diagnosis of exclusion. Central, systemic, and toxic causes of hyperthermia and rigidity must be excluded, as well as other causes of rhabdomyolysis and altered mental status.

Recent report suggests that alkalinized fluids or even bicarbonate loading may be of particular benefit in preventing renal failure.[8] Our case presented with full blown acute renal failure prior to admission; so preventive strategy could not be initiated. Intensive medical care should include careful monitoring for complications (Table-2)[9], and may involve support of cardiac, respiratory and renal function.

NMS is a self limited disorder, and in many case, medical management and cessation of antipsychotic medication may suffice to reverse the symptoms. There is no general consensus on specific pharmacological treatments for NMS. The role of intravenous dantrolene sodium therapy, used widely in malignant hyperthermia, is unclear. Still it is administered to reduce body temperature and to relax peripheral muscles. Bromocriptine, a dopamine agonist, usually improves muscle rigidity within a few hours, followed by a reduction in temperature and an improvement in blood pressure. Amantadine and levodopa-carbidopa have been used successfully to reduce hyperthermia in patients with NMS.[10] Our patient improved clinically after use of Bromocriptine and Levodopa-carbidopa. Treatment for NMS must be continued for 2-3 weeks until symptoms remit.

NMS is under reported in critical care practice; though the use of Haloperidol, Olanzapine, and Risperidone, for delirium, and Metoclopramide (dopamine blocking) and Prochlorperazine (a neuroleptic agent used for emesis) as antiemetic, is common in ICU. Concomitant uses of sedatives and muscle relaxants in ICU patients may obscure mental status changes, rigidity and tremor. Thus it may only manifest as hyperthermia and autonomic dysfunction. Increased familiarity with the features of the NMS and studies of the incidence and pathogenesis of this disorder should lead to more effective management and decreased morbidity. Our patient survived NMS but was suffering from complication e.g. acute renal failure and pneumonia with respiratory failure. Unfortunately his life was cut short because of withdrawal of ventilatory support and hemodialysis by his family.

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