

ATYPICAL PRESENTATION OF NEUROLEPTIC MALIGNANT SYNDROME: A DIAGNOSTIC DILEMMA

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is an idiosyncratic, fatal complication of antipsychotic treatment. We report the case of a 37-year-old woman who was on medications for cardiac problems and presented with acute onset of manic symptoms of four days duration. She was admitted due to presence of altered sensorium. Hypokalemia was detected. She was started on Tab. Risperidone and intramuscular Haloperidol for her behavioral problems. However, the delirium worsened and she developed rigidity. Investigations revealed elevated creatinine phosphokinase (CPK) and worsening hypokalemia. In view of muscular rigidity, elevated CPK and worsening delirium even after correcting hypokalemia, a diagnosis of NMS was considered. Her symptoms improved once Risperidone and Haloperidol were stopped and treatment for NMS was instituted. This case demonstrates that early or impending NMS can have atypical presentations, pose a diagnostic dilemma and delay treatment; and highlights the importance of early diagnosis and treatment of NMS.

Keywords: neuroleptic malignant syndrome, antipsychotics, extrapyramidal symptoms

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an idiosyncratic life-threatening complication of antipsychotic treatment. It was first described by Delay and colleagues after the introduction of neuroleptics in 1960. They called it the “akinetik hypertonic syndrome”. Although estimates of incidence once ran as high as 3%, recent data shows an incidence of 0.01%-0.02%.¹ This may be due to an increased awareness about the disorder, more conservative prescribing patterns, and a preference for atypical antipsychotics. Earlier diagnosis of

NMS may prevent its progression to its more fulminant lethal episodes.

We present the case of a patient who had an atypical presentation of NMS characterized only by rigidity, elevated serum creatinine phosphokinase (CPK) and altered sensorium.

CASE REPORT

A 37-year old, married lady presented with a history of acute onset of behavioral symptoms characterized by pervasive irritable mood, over-talkativeness, decreased sleep and psychomotor agitation of four days duration. She also had a history of altered

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sensorium, irrelevant talk and drowsiness of one-day duration, and hence we admitted her. She had past history of a manic episode with psychotic features seven months back, which had lasted a week. It had resolved on treatment with Tab. Risperidone, but she had discontinued it once the symptoms resolved. There was also a history of rheumatic fever 18 years back, for which she was on prophylaxis with Tab. Penicillin G 800 mg/day since then. Mitral valve replacement was done 14 years ago. She also had the history of a cerebrovascular accident one and half years back, from which she had recovered fully. At the time of admission, she was on Tab. Verapamil 40 mg TID, Tab. Digoxin 0.25 mcg OD (5/7), Tab. Furosemide 20 mg OD, Tab. Warfarin 5mg/6mg on alternate days, and Tab. Aspirin 75 mg OD.

She was not co-operative for detailed mental status examination, and had disorientation to time and place and impaired attention and concentration. Psychomotor activity was increased, talk was irrelevant, and mood was irritable. On physical examination, pulse rate was 88 per minute and blood pressure 140/100 mm of Hg. She was afebrile. Systemic examination revealed no abnormalities. At the time of admission, her serum Potassium was 3.4 meq/dl and INR was 2.90.

Tab. Risperidone was started at the dose of 1 mg/day and was increased to 1.5 mg/day. Three doses of Inj. Haloperidol 2.5 mg were given intramuscularly, on SOS basis, to control her agitation.

However, her delirium worsened and she developed rigidity by third day. On investigation, serum CPK was elevated (3687 U/L) and hypokalemia was worsening (2.8 meq/dl). A provisional diagnosis of NMS was made since her delirium was worsening and as she had developed rigidity and elevated serum CPK levels following administration of antipsychotics.

Risperidone and Haloperidol were stopped and she was started on Tab. Bromocriptine 2.5 mg TID,

Tab. Lorazepam 4 mg/day, and Tab. Trihexyphenidyl 2 mg twice daily. Tab. Furosemide was withheld in view of hypokalemia. With oral supplementation of potassium, her serum potassium level normalized in a day. In spite of correcting serum potassium levels, her delirium persisted. Other supportive measures including intravenous hydration were given and serial monitoring of serum CPK and potassium levels was done.

CPK levels normalized in one week, and by that time the delirium too resolved. Bromocriptine was continued for one more week and then tapered and stopped. To address her mood symptoms, Tab. Sodium Valproate was started and the dose was hiked to 1200 mg/day. We did not re-challenge her with antipsychotics.

DISCUSSION

NMS is a diagnosis of exclusion. Levenson's criteria is commonly used in clinical settings (Table 1).² According to it, all the three major, or two major plus three minor criteria, if suggested by clinical history, indicate a high probability of NMS. DSM-5 describes hyperthermia, diaphoresis, rigidity, elevated CPK, altered consciousness etc. as the diagnostic features of NMS, and specify that these features should not be better accounted for by a substance induced, neurological or general medical condition.³

Table 1: Levenson's clinical criteria for NMS

Major	Minor
<ul style="list-style-type: none"> • Fever • Rigidity • Elevated creatinine phosphokinase concentration 	<ul style="list-style-type: none"> • Tachycardia • Abnormal arterial pressure • Diaphoresis • Leukocytosis • Altered sensorium • Tachypnea

A similar case was reported by Paul et al. where a 36-year-old woman presented with fever, elevated serum CPK levels, altered mental status, and autonomic instability.⁴ She was on various medications including lithium, sertraline, venlafaxine, bupropion, lamotrigine, loxapine and trazodone. She was initially treated as a case of serotonin syndrome, but no improvement was observed. Later, a diagnosis of NMS was considered and she improved once the treatment for NMS was instituted. Seitz reported case of a 51-year-old man with schizophrenia who was on clozapine, risperidone and clonazepam and presented with rigidity, altered sensorium, urinary incontinence, moderately elevated CPK and leukocytosis.⁵ The provisional diagnosis made was exacerbation of psychosis. The patient's condition worsened, with rising CPK levels and fever. A diagnosis of NMS was subsequently made and specific treatment was instituted.

In our case, the patient had rigidity and elevated CPK from Levenson's major criteria, and altered sensorium from the minor criteria. The initial altered sensorium might have been due to hypokalemia, but the worsening of delirium occurred with the onset of NMS. The diagnosis of NMS was considered since her delirium was worsening despite correction of serum potassium levels, and as she developed rigidity and elevated CPK levels following antipsychotic administration. Even though she had an atypical presentation and did not meet the diagnostic criteria, we considered a provisional diagnosis of NMS and instituted appropriate treatment. Once the antipsychotics were stopped and treatment for NMS was instituted, her symptoms resolved completely.

Our case illustrates one of the many clinical presentations possible in NMS. Diagnosing NMS poses a challenge when the patient presents without marked abnormalities of temperature or muscle tone.⁶ In a review of 115 cases of NMS, Addonizio et al. observed that extrapyramidal symptoms (EPS) preceded fever in 59% of the cases.⁷ EPS and fever

appeared concurrently in only 23%, and 9% had no muscle rigidity. Delayed onset or absence of fever has also been reported in NMS.^{8,9} In approximately 10-40% of cases, either fever and rigidity will both be attenuated or only one will be present.^{2,7} When such hallmark symptoms are absent, there is high chance for a wrong diagnosis and delay in diagnosis of NMS. Timely and accurate diagnosis of NMS avoids further exposure to neuroleptics and allows early initiation of correct treatment. Due to the heterogeneity in presentation, it has been suggested that a spectrum of neuroleptic toxicity exists, with mild EPS at one end and full blown NMS at the other.¹⁰ This construct may be useful as in some patients mild EPS may represent incipient or prodromal NMS.

However, DSM 5 states that the symptoms should not be the result of a neurological or general medical condition or a substance. The onset of delirium in our case was before administration of antipsychotics, and its probable underlying cause was hypokalemia we detected at the time of admission. Worsening of her delirium may have been due to the falling potassium levels, and it also coincided with the administration of neuroleptics. She also had elevated CPK levels, but even that cannot be considered pathognomonic of NMS. Even though the progression of symptoms could be explained by an existing medical condition, the development of rigidity and the worsening of delirium following administration of antipsychotics warranted a high index of suspicion for NMS.

Numerous case reports and retrospective analyses support the concept of atypical NMS. Our case highlights the fact that a possibility of NMS should be considered when acute changes happen in the medical status of patients treated with antipsychotics even when the symptoms do not satisfy the diagnostic criteria for NMS, and that we should be vigilant about the likelihood of atypical presentations.

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