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Neuroleptic Malignant Syndrome and Elevated CSF Protein with Quetiapine: Case Report and Review of Literature

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Abstract Neuroleptic malignant syndrome (NMS) is a well-known complication of dopaminergic blockade. While there have been many case reports on Quetiapine-induced NMS, cerebrospinal fluid (CSF) abnormalities have never been documented. We report this case of bipolar affective disorder who had a previous history of Risperidone-induced parkinsonian rigidity. He presented to us 20 days after increasing lithium dose and starting Quetiapine and lamotrigine for an acute episode of mania. He had coarse tremors at rest, hyperthermia, altered sensorium and elevated creatine phosphokinase (CPK). CSF analysis showed elevated protein with no cells. A provisional diagnosis NMS was made and he was given bromocriptine. Patient's hyperthermia resolved and CPK normalized with this treatment. He was subsequently discharged and is in follow up for his bipolar disorder.

Keywords: *Neuroleptic malignant syndrome (NMS), atypical antipsychotics, Quetiapine*

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1. Introduction

Neuroleptic malignant syndrome is a potentially life-threatening condition first described by Delay et al [1] in 1960 with haloperidol. The prevalence of NMS has regional variability with one meta-analysis done in 2007 put an estimate of 0.991 cases per thousand people [2]. The clinical features include to hyperthermia, tremors, rigidity, diaphoresis and autonomic instability.

Quetiapine-induced NMS or extrapyramidal (EPS) symptoms are rare in placebo-controlled trials [3]. There was isolated elevated protein in CSF with normal glucose level and nil cells in our patient. While abnormalities of neurometabolites like 5 -HIAA (5-hydroxy indole acetic acid) and HVA (Homovanillic acid) have been reported in CSF of patients with NMS [4] elevated protein levels are not reported per se. Our case also had hypernatremia after resolution of NMS. While there is a case report on NMS with olanzapine with severe hypernatremia [5] there is no case in literature implicating Quetiapine with hypernatremia.

To our knowledge, this is the first case report in which Quetiapine-induced NMS is associated with elevated CSF protein levels.

2. Case Report

A 24-year-old male, known case of bipolar affective disorder-mania since 2009, maintained on valproate 750mg sustained release (SR) once per day, Lithium 800mg twice daily, Tab. Clonazepam 0.5mg if needed presented to the All India Institute of Medical Sciences (AIIMS), New Delhi with a history of tremors for last 1 month which were exacerbated over last 5 days along with nausea. He had started passing urine and feces on the bed for the same duration. There was decreased responsiveness for last 2 days. He developed altered sensorium over last 24 hours. On enquiring from the patient's father; he had an episode of mania around 20 days back after which valproate was stopped and Quetiapine SR 400 mg with lamotrigine 200 mg per day was added; lithium was increased to 1750 mg per day in 3 divided doses. He had continued to take these medications till 5 days before presentation. There was no history of raised temperature initially recorded, seizure, decreased urine output, focal neurological deficit, head trauma, abuse of any psychotropic drug or intentional drug overdose.

At the time of initial evaluation, his vitals were stable as was his blood sugar level.

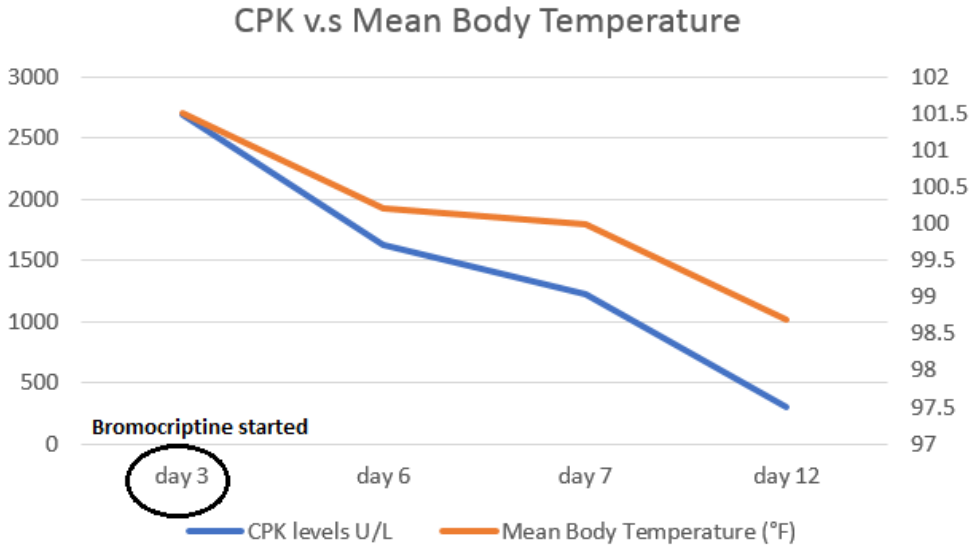
Further examination revealed bilateral lower lobe crackles with normal vesicular breath sounds. There were purposeless eye movements with bilateral constricted pupils; reactive to light. There was generalized rigidity and coarse tremors at rest predominantly of bilateral lower limbs. There were multiple healed cuts over the left hand. A urine toxicology screen was done which was negative for all substances tested. Non-contrast Computed Tomography (NCCT) scan of the head was normal.

The patient was shifted to Intensive Care Unit (ICU) where he was intubated in view of altered sensorium after giving 10mg of midazolam and 150ug of fentanyl.

A provisional diagnosis of acute kidney injury with altered sensorium was made. Probable causes of altered sensorium that were kept were meningoencephalitis, lithium toxicity, unknown poisoning, septic or neuroleptic malignant syndrome.

He was started on empirical antibiotics suspecting infection with the potential cause being aspiration pneumonia due to altered sensorium; chest X-ray was, however, normal. High-grade remittent elevated body temperature 101-102°F was recorded in ICU which decreased with antipyretics but never touched the baseline. There was generalized rigidity with persistent tachycardia and profuse diaphoresis. Serum lithium levels were obtained next morning which was 0.72mmol/l (0.4-0.8mmol/l). Despite antibiotic use, his fever did not resolve nor his rigidity decreased.

In view of generalized rigidity, hyperthermia not responding to antipyretics with raised creatine and CPK, a diagnosis of the neuroleptic malignant syndrome was made. Dantrolene was not available in the hospital, therefore, bromocriptine 5 mg was given thrice a day from day 3 of admission. His hyperthermia responded dramatically; CPK and creatinine gradually resolved (Graph 1). There was improvement in sensorium on day 5 and he was subsequently extubated. On day 10 of admission, he was shifted out of the ICU and all antibiotics were stopped. Laboratory values during the patient's hospital stay were as in Table 1. The patient was shifted to the psychiatry ward for initiation of treatment of the bipolar affective disorder.



Graph 1. CPK v/s Mean body temperature recorded

Table 1. Laboratory values of patient

	Reference Range#	Day 1	Day 3	Day 7	Day 12
Hemoglobin (gm/dl)	12-15	10.5	9.7	7.9	8.4
TLC (cells/ul)	4,000-11,000	15500	20300	11800	7700
Platelets (cells/ul)	2,50,000-4,00,000	1,71,000	1,38,000	2,17,000	2,45,000
Urea (mg/dl)	10-50	51	46	52	42
Creatinine (mg/dl)	0.5-1.8	2.1	1.7	1.3	1
Ionized calcium (mmol/l)	1.10-1.40	1.20		1.21	1.20
Phosphate (mg/dl)	2.5-4.5		4.6	8.1	7.6
Uric acid (mg/dl)	2-7.4		11	6.5	6.1
Sodium	130-149	139	141	157	157
Potassium	3.5-5	5.8	5	4.4	4.5
SGOT (IU/L)	0-50		31	77	62
SGPT (IU/L)	0-50		39	66	62
ALP (U/L)	80-240		1305	941	684
LDH (U/L)	200-420			544	
CSF					
Total cells (per mm^3)	0-5	0			
Protein (mg/dl)	15-45	47			
Glucose (mg/dl)	45-80	78			
Procalcitonin (ng/ml)	<0.15	3			

3. Discussion

Antipsychotic drugs can be divided into types based on the mechanism of action. Typical antipsychotics cause predominantly dopamine blockade and have more chances of precipitating NMS while atypical antipsychotics like risperidone have alternative mechanisms and therefore have fewer chances of the same. There are case reports of NMS associated with the use of non-neuroleptic drugs, like Carbamazepine [6], Metoclopramide [7] and Lithium [8,9]. There are numerous case reports describing NMS with atypical antipsychotics. There are various criteria for the diagnosis of NMS [10,11,12,13] with DSM-V [14] definition being the latest one. It necessitates the presence of hyperthermia oral temperature >38°C on at least two occasions) rigidity, CPK elevation > 4 times upper limit of normal, altered mental status, and autonomic dysfunction in the form of tachypnea (>50% from baseline), tachycardia (>25% from baseline), blood pressure elevation systolic or diastolic 25% above baseline), urinary incontinence and diaphoresis, other extrapyramidal symptoms (EPS), mental status changes, and laboratory alterations. Our case had tremor, rigidity, altered sensorium, diaphoresis with raised temperature; leukocytosis, incontinence, blood pressure fluctuations with elevated CPK concordant with the diagnosis. Moreover, history of initiation of new atypical antipsychotic with dramatic improvement with bromocriptine indicated that NMS was the likely diagnosis in this patient. The cause of raised lactate dehydrogenase (LDH), CPK and creatinine is probably increased muscle breakdown due to tremors and rigidity. Our patient had important risk factors for developing NMS. A meta-analysis [15] published in 2017 (identifying observations from 1998 to 2014) showed that NMS patients are more likely to be males (75%) with a peak incidence at age 20-25 years. About 25% cases of NMS with this drug had a history of EPS symptoms due to other antipsychotics. Our case had a history of drug-induced parkinsonism from 2010 to 2013 while taking risperidone and had been prescribed trihexyphenidyl. While trihexyphenidyl was discontinued in 2013, he continued to take risperidone for another 1 year without any extrapyramidal symptoms. The differentials of NMS [16] are diverse and sometimes symptoms may overlap. In fact, it has been argued that NMS is a diagnosis of exclusion. Table 2 lists the differential diagnosis considered.

Table 2. Differential diagnosis of NMS

Infections	Meningoencephalitis
Psychiatric	Agitated delirium Idiopathic malignant catatonia Midbrain organic lesions
Toxin	Lithium toxicity Serotonin syndrome Amphetamine abuse Salicylate toxicity Organophosphate toxicity Alcohol withdrawal
Heat stroke	

Organic lesions and the infectious cause were ruled out by NCCT head and CSF respectively. Serum lithium levels done were normal as was the toxicology screen. The patient had been initiated on Quetiapine sustained-release 400 mg tablet 20 days before symptoms began. NMS associated with atypical antipsychotics is known to precipitate in about 30 days from the start of treatment and around 60% patients are on concomitant psychotropic medications [14]. Our patient was receiving lamotrigine, lithium, and clonazepam simultaneously, the possible interaction cannot be ruled out since both lithium and lamotrigine are associated with NMS [7,9,18].

We reviewed the literature and found that various similar reports of Quetiapine-induced NMS [8,19]. Quetiapine-induced NMS is postulated to be due to its inhibition of noradrenaline reuptake, histaminergic and α-adrenergic antagonism, and serotonin-related effects [20]. There was isolated elevated protein in CSF with normal glucose level and nil cells in our patient.

Our case also had hypernatremia after resolution of NMS. While there is a case report on NMS with Olanzapine with severe hypernatremia [5] there is no case in literature implicating Quetiapine with hypernatremia. It could possibly be due to dehydration secondary to NMS induced diaphoresis

4. Conclusion

Atypical antipsychotics can cause neuroleptic malignant syndrome which can mimic many other clinical conditions. A strong suspicion, therefore, is must whenever these drugs are administered, dosage changed, or other psychotropic drugs are added. Temporal association with these changes along with relevant investigation help clinch the diagnosis.

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