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Letter to the Editor

Atypical neuroleptic malignant syndrome – A case report

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a potentially fatal adverse effect of antipsychotics. Atypical presentation of NMS with drugs which are not potential D2 blockers raises question for an alternative hypothesis for NMS. A 30 year old male presented with irritability, assaultive behavior, persecutory delusion and auditory hallucination for three days. Past history of 3 similar episodes. 1st episode preceded by fever and associated with cerebral edema. Subsequent episodes not preceded by fever and patient was treated with Risperidone and Olanzapine. After admission patient was started on Risperidone along with THP when he had fever, tremors, altered sensorium and rigidity at 3 mg dose. After stopping Risperidone fever and rigidity improved with worsening of psychotic symptoms. Following this Olanzapine was started and very gradually uptitrated to 7.5 mg when patient had recurrence of fever and disorientation without tremors and minimal rigidity. Both the instances blood investigations including CPK levels were normal except for thrombocytopenia and leucopenia. Provisional impression of NMS was made in both instances. After stopping Olanzapine fever subsided with improvement of blood counts. Following this patient had catatonic symptoms for which patient received 9 sessions of Electroconvulsive therapy (ECT). In atypical presentations of NMS, hyperthermia and muscle rigidity may be absent, posing diagnostic dilemma. So there is a need for broadening the diagnostic criteria and NMS must be considered with a high index of suspicion.

1. Introduction

Neuroleptic malignant syndrome (NMS) is a potentially fatal adverse effect of antipsychotics (AP). An annual incidence of NMS of 0.17–32/1,000 and 0.064/1,000 is estimated for patients receiving typical AP and atypical AP respectively (Belvederi Murri et al., 2015). NMS is widely accepted to be resulting from profound dopamine receptor blockade in nigrostriatal and hypothalamic region. But atypical presentation of NMS with drugs like aripiprazole and clozapine which are not potential D2 blockers raises question for an alternative hypothesis for NMS. Serotonergic, adrenergic, and cholinergic receptors take substantial part in extrapyramidal motor functions, thermoregulation, muscle metabolism and mental status which may also play role in NMS (Picard et al., 2008; Uvais, 2017). It has been seen that incidence of extrapyramidal symptoms(EPS) is more with Fluoxetine and Haloperidol than Haloperidol alone which was postulated to be due to the increased serotonergic activity (Halman and Goldbloom, 1990).

With this background, a case of atypical presentation of NMS in a patient receiving atypical AP highlighting nosological challenges is reported.

2. Case report

A 30 year old male presented to our out-patient department with irritability, assaultive behaviour and smiling and muttering to self for three days. Past history of three episodes of similar complaints was noted. The first episode was preceded by fever and was associated with cerebral edema (in Computerized Tomogram (CT)). He was diagnosed with Viral encephalitis and managed with Acyclovir and Olanzapine 25 mg. Subsequent episodes were not preceded by fever and patient was treated with Risperidone upto 6 mg and Trihexyphenidyl (THP) 10 mg. Patient was found to need high dose of THP because of high susceptibility to extra-pyramidal symptoms (EPS).

Patient was admitted in view of risk of harm to self and others. Mental status examinations (MSE) revealed delusion of persecution and auditory hallucinations with a score of 36 on Brief Psychiatric Rating Scale (BPRS) and 0 on Bush- Francis Catatonia Rating Scale (BFCRS). Patient was started on Risperidone 2 mg and THP 2 mg. Risperidone was increased to 3 mg on day 2 of admission. Patient was found to have worsening of tremors and rigidity. On Day 3, patient had fever of 101 °F and appeared drowsy and perplexed. Despite Acetaminophen 2000 mg, low grade fever persisted for the next two days. Creatinine Phosphokinase (CPK) was 38. Complete Hemogram, peripheral smear, dengue serology, blood and urine culture, urine for myoglobulin, renal, liver and thyroid function tests were found to be normal. So, a tentative diagnosis of NMS was made and all psychotropic medications were stopped. Even on stopping AP, patient had episodes of uprolling of eyes with truncal and neck rigidity which got relieved with Promethazine injection. Post four days of stopping antipsychotics, fever and rigidity improved with worsening of psychotic symptoms.

As agitation could not be managed by benzodiazepines alone, Olanzapine was started at 2.5 mg. Olanzapine was gradually uptitrated at rate of 2.5 mg every 3–5 days under cover of 6 mg THP. However when Olanzapine was increased to 7.5 mg, patient had recurrence of fever of about 106 °F and perplexity with disorientation. There were no tremors with minimal rigidity. Again, workup for fever as described previously including CPK levels were done. They were normal except for thrombocytopenia (1.25 lacs/mm^3) and leucopenia (2370/mm^3). Magnetic Resonance Imaging revealed Bilateral Hippocampal atrophy. Anti- N-methyl-D-aspartate antibodies were found to be negative. No focus of fever could be found out. Medicine opinion was sought and provisional

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impression of NMS was made. All the antipsychotics were stopped and he was started on oral Bromocriptine at 7.5 mg and intravenous acetaminophen at 4 g per day. Patient's fever had subsided with improvement of blood counts after three days of medication. However, he started having transient catatonic symptoms which gradually worsened to compromise of food intake despite being on 18 mg Lorazepam with a BFCRS of 6 and BPRS of 34. Following which, patient was referred for Electroconvulsive therapy (ECT). Patient received 9 sessions of ECT following which his symptoms improved. Patient was also started on Aripiprazole 5 mg which was gradually uptitrated to 15 mg over a period of 2months and was relatively maintaining well till 4 months post discharge with a BPRS of 26 and BFCRS of 0 when he was lost to followup.

3. Discussion

Though classical NMS is described with features of hyperpyrexia, extrapyramidal symptoms, autonomic instability and altered mental status, it might not always hold true as in current case. Unusual presentations of NMS have been most commonly described in patients receiving atypical AP. In atypical presentations of NMS, hyperthermia and muscle rigidity may be absent or may develop slowly with lesser intensity (Picard et al., 2008). Our patient had only minimal rigidity with Olanzapine. This is in concordance with previous findings reporting 32% of Olanzapine treated patients not exhibiting EPS during NMS (Ananth et al., 2004). In comparison to extant literature on patients developing NMS with Risperidone or Olanzapine, our case was comparatively younger (compared to mean age of 48.3 and 48.5 years for risperidone and olanzapine respectively) and received AP for shorter duration (< 1 week) (compared to 46.3 and 135 days for risperidone and olanzapine respectively (Ananth et al., 2004). A previous case report also indicates onset of fever before onset of EPS and autonomic instability with Olanzapine (Ali et al., 2017). Atypical presentations of NMS have also been reported with Aripiprazole and Clozapine. NMS with Aripiprazole was reported to have only diaphoresis, tremors and elevated CPK with no hyperpyrexia or rigidity (Tibrewal et al., 2017). NMS was reported after cessation of Clozapine with catatonic symptoms, diaphoresis and elevated CPK (Ingole et al., 2017). Overdose of Asenapine also was to be associated with atypical NMS (Das et al., 2017). However, in all these case reports CPK was elevated in contrast to our patient.

Another atypicality noted in this case was presence of thrombocytopenia and leucopenia in contrast to the expected leukocytosis. However, case reports of thrombocytopenia and leucopenia in patients with NMS exist (Ghani et al., 2000; Ray, 1997). The case also demonstrates the need for careful history taking in order to facilitate early diagnosis as early recognition and prompt discontinuation of offending agent combined with supportive care could improve majority of cases (Velamoor, 2017). In our case when anti-psychotics were up-titrated, the first symptoms were fever and disorientation in both the instances. In more than 80% of cases, altered mental status presenting as confusion, catatonia, delirium or agitation precede the onset of systemic signs of NMS posing diagnostic dilemma (Shah et al., 2012). Further, our patient was on high dose of benzodiazepines, which further added to diagnostic difficulty.

In this case, considering the prior history of encephalitis we can also consider the possibility of post encephalitic catatonia presenting as malignant catatonia. Intolerance to antipsychotics (Lejuste et al., 2016) and persistence of catatonic symptoms despite withdrawing of antipsychotics may also be suggestive of post encephalitic catatonia. However, onset of fever after initiation of antipsychotics and absence of cerebral edema during the current episode were the points against it.

The current case report highlights the need for broadening the diagnostic criteria for NMS. In the first instance of NMS with Risperidone, patient had fever, rigidity and tremors. But in the second instance when an antipsychotic with low propensity for EPS was started and dose was escalated, there was hyperpyrexia with only minimal rigidity. Clear temporal relationship was noted between onset and offset of fever with up-titration and stopping of AP respectively. We could not make a diagnosis of NMS by using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM IV-TR) criteria. Limitations of the current diagnostic criteria has also been highlighted in literature previously (Menon et al., 2017).

NMS is associated with high morbidity and mortality (Modi et al., 2016). Inability to diagnose NMS by current nosological systems must not deter the physician from treating atypical presentations. Hence, clinicians must be vigilant about atypical presentations of NMS without rigidity. Diagnosis of NMS must be considered with a high index of suspicion in patients with onset of hyperpyrexia and confusion with initiation/uptitration of AP.

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