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Case report

Neuroleptic Malignant Syndrome Associated with Venlafaxine: A Rare Side Effect

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is an infrequent but a potentially life-threatening emergency, associated with the use of neuroleptic and antipsychotic medications. It is characterised by tetrad of symptoms including fever, rigidity, altered mental status and autonomic dysfunction. Few cases of NMS have been reported to be caused by use of Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin Norepinephrine Reuptake Inhibitor (SNRI).

NMS was first described in 1960 with the use of Haloperidol. It has been associated with virtually all neuroleptics including newer atypical antipsychotics. The incidence rate ranges from 0.02% to 3%. However, the incidence rate as decreased with newer neuroleptics to 0.01% to 0.02%. Due to its life-threatening nature, NMS requires prompt diagnosis and treatment, ruling out similar conditions such as Serotonin Syndrome and Malignant Hyperthermia.

A 60-year-old female was admitted with one week of paranoia, hallucination, incomprehensible speech and a background history of Parkinson disease, anxiety and depression. She was on Sinemet plus 25/100 five times a day. Amantadine 100 mg once a day, Clonazepam 500 mg at night, Venlafaxine 150 mg twice a day. Her Amantadine and Sinemet plus was stopped 1/52 prior to admission in community and Venlafaxine was stopped on admission. Few days later she developed persistent hyperthermia, raised CK and Lactate. A diagnosis of NMS was made, and improvement was seen with Dantrolene along with supportive measures. Patient was stabilised for discharge and her Venlafaxine was reintroduced. She had a relapse of her symptoms with high grade fever, confusion and rigidity. This case emphasizes the need and importance of re-introducing non-neuroleptic medications at an early stage of recovery which resulted in relapse of NMS, a rare side effect of venlafaxine.

Keywords: Venlafaxine rechallange; Neuroleptic malignant syndrome; Malignant hyperthermia

INTRODUCTION

Neuroleptic Malignant Syndrome (NMS) is a life-threatening idiosyncratic reaction to antipsychotic drugs which is characterized by fever, muscle rigidity, altered mental status, and autonomic dysfunction. Venlafaxine has fewer side effects; it can be used to treat NMS. Venlafaxine is used to treat depression. It may improve your mood and energy level, and may help in restoring the daily activities. Venlafaxine is known as a Serotonin-Norepinephrine Reuptake Inhibitor (SNRI). It works by helping to restore the balance of certain natural substances (norepinephrine and serotonin) in the brain.

CASE STUDY

60-year-old was admitted with one-week history of paranoia, hallucination, agitation, falls and seemed more confused than normal. She had history of Parkinson's disease, anxiety and depression. Her Parkinson's disease was well controlled on Sinemet and half Sinemet along with Amantadine which was stopped a week ago prior to admission by Parkinson's nurse specialist. She was also on Venlafaxine for her depression. She was due to see a psychiatrist but the visit was delayed due to the COVID pandemic. On admission to ED, she was combative, agitated which made it difficult to get any observations or perform clinical examination. ED team managed to get her cannulated along with a VBG sample. She received 1 mg of

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Lorazepam IV in ED which calmed her down. Subsequently, she underwent full observations and clinical examination which did not show any abnormality. Her urine test came back normal. No acute findings noted on ECG. She also had head CT which showed no acute intracranial abnormality. So far, the only abnormality noted was in her VBG which was lactate and high at 3.1. She was given IV fluids in ED and referred to the medical team.

On admission to medical ward, she was treated as sepsis with differential including UTI or encephalitis. She was started on broad spectrum IV antibiotics with sepsis bundle. She had additional investigations including blood and urine culture which all came back negative. She was referred to neurology team to rule out encephalitis. A lumbar puncture and MRI head were performed. All came back as normal.

Patient did not improve on sepsis protocol instead remained quite rigid, confused. On day 5 of admission, she became hyperthermic with temperature of 38.9 degrees Celsius and developed a brief seizure. She was started on Phenytoin and had repeat blood cultures with full routine bloods including CK this time in keeping with differentials of Malignant hyperthermia, Serotonin Syndrome and Neuroleptic Malignant Syndrome. Her Venlafaxine was stopped, and she was put on Rotigotine 2 mg patch for her Parkinson's. Her routine bloods all came back as completely normal with no signs of infective picture. Her electrolytes, LFTS and C. Ca were all within range including CRP remaining <1, throughout her admission. Her CK came back as 739 u/l which went up to 2584 u/l on 3rd day of her hyperthermia.

The patient was treated with Dantrolene IV 110 mg (2 mg/kg) along with supportive cooling measures and IV fluids. She had RIG tube inserted to facilitate her Parkinson's medication. After almost 10-12 days patient showed progress and her symptoms resolved. She became orientated and started engaging in rehabilitation therapy. She was optimised for discharge with review of her medication and was restarted on her Venlafaxine. After 48 hrs of re-introduction of Venlafaxine, she became hyperthermic again with temperature of 38.9 degree Celsius reaching up to 40 degree Celsius with altered mental status, autonomic instability and rigidity. She had full sets of bloods repeated including, COVID, B C/S, urine C/S, and CK. Again, the only abnormality noted was raised CK of 1146 u/l. Treatment was initiated for relapse of Neuroleptic Malignant Syndrome, related to her antipsychotic medication, with IV Dantrolene, cooling and supportive measures. Her Venlafaxine was stopped; patient became better and was finally discharged to her own home with carer support (Table 1).

Drug administration	Creatine kinase (CK) levels in blood
Rotigotine 2 mg	1st day of administration 739 u/l
	3rd day of administration 2584 u/l
Dantrolene IV 110 mg	After 10-12 days of administration 1146 u/l

Table 1: Creatine kinase levels in the blood after administration of different drugs.

DISCUSSION

NMS, which is thought to be an idiosyncratic drug reaction, is a rare but potentially lethal complication of treatment with neuroleptics. According to one theory, decreased dopamine activity in the Central Nervous System (CNS), either from of dopamine D2-receptors or decreased availability of dopamine itself, plays a role in the pathogenesis of NMS [4]. Manifestations of NMS may include autonomic instability, hyperpyrexia, altered mental status, and extrapyramidal reactions [5]. The appearance of these symptoms, especially extrapyramidal reactions in patients receiving antipsychotic drugs, should alert physicians to include NMS in the differential diagnosis. Although extrapyramidal reactions or NMS are most likely to be associated with the use of high-potency neuroleptics, these uncommon side effects have been reported to be associated with SSRI use [1, 2]. Serotonin's inhibitory action on SSRI-induced extrapyramidal dopamine activity has been proposed to contribute to the aetiology [6].

Some authors have also hypothesized that individuals who develop extrapyramidal symptoms after SSRI use may actually have preclinical Parkinsonism [7, 8]. Venlafaxine is an SNRI. There have been an increasing number of reports of extrapyramidal reactions in association with venlafaxine [9,10]. It has been reported to induce NMS when combined with trifluoperazine [3]. Cassidy and O'Kearne considered that absence of altered sensorium and a relatively benign course, as in the above-reported patient, are more likely to be serotonin syndrome than NMS [11].

NMS and serotonin syndrome are difficult to differentiate because of their overlapping clinical features. The diagnostic criteria for serotonin syndrome as proposed by Sternbach are: Recent change of a potent serotonin agent; no history of substance abuse or infectious or metabolic disease; absence of treatment with any antipsychotic drug; and >3 of the following symptoms:

1-change in the finding of the mental status, 2-agitation, 3-myoclonus, 4-hyperreflexia, 5-diaphoresis, 6-shivering, 7-tremor, 8 diarrhoea, 9-unco ordination, and 10-fever [12].

Although serotonin syndrome has been increasingly recognized as a possible adverse event in patients who receive SNRIs like venlafaxine, it is also possible that NMS may occur through their serotonergic inhibition of central dopaminergic activity, a mechanism similar to extrapyramidal adverse drug reactions.

CONCLUSION

Patient mentioned in this case report shared many overlapping features of drug-induced fever like serotonin syndrome and MH, but she did not receive any volatile anaesthetics or succinylcholine, and the relatively gradual onset and severe

clinical manifestations favoured a diagnosis of NMS rather than serotonin syndrome. Based on these considerations, the patient was diagnosed with NMS rather than other drug-induced fever due to the presence of extrapyramidal symptoms with severe rigidity, severe hyperthermia, rhabdomyolysis with elevated CK, leucocytosis with abnormal liver function, and altered mental. Such diagnosis of drug is difficult to establish. It can only be done by withdrawing the drug and subsequent re-challenge it.

In summary, the use of venlafaxine may be implicated in the development of NMS in Patients with clinical manifestations of Parkinsonism, possibly due to its serotonergic inhibition of the central dopaminergic system. Greater awareness of this potential side effect may facilitate early recognition and treatment to decrease its morbidity.

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