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ATYPICAL NEUROLEPTIC MALIGNANT SYNDROME ASSOCIATED WITH MIRTAZAPINE USE

Talha Ağaç[1], Hasan Gökçay[2] & Mustafa Solmaz[1]

1 Department of Psychiatry, University of Health Sciences, Bagcilar Training and Research Hospital, Istanbul, Turkey
2 Psychiatry unit, Şarkışla State Hospital, Sivas, Turkey

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a potentially fatal complication of neuroleptic drug use. Its incidence is between 0.2%-3% (Piacenza et al. 2021). The NMS clinic's onset, appearance, progression, and end are multifaceted. NMS can be seen clinically with many findings including autonomic instability, creatine phosphokinase (CPK) elevation, hyperthermia, rigidity, leukocytosis, and changes in consciousness (Miranda et al. 2011). When NMS develops without one of the main symptoms, such as hyperthermia or rigidity, it is called atypical NMS (Szota et. al 2022). Although various hypotheses have been proposed for the etiology of NMS, the exact cause is unknown. Mostly, dopamine antagonists have been used 72 hours before the onset of symptoms. NMS has also been reported with dopamine agonist withdrawal or dose reduction (Piacenza et al. 2021, Stevens 2008). Combined use of antipsychotics and antidepressants is also a risk factor for the development of NMS (Stevens 2008, Szota et al. 2022). Although NMS cases of NMS due to antidepressant use such as SSRI, SNRI and Tricyclic have also been reported (Miranda et al. 2011, Lu et al. 2006, Haddow et al. 2004). We report a case of atypical NMS in a 72-year-old male who developed after the initiation of mirtazapine for a depressive mood disorder.

CASE

A 72-year-old male patient was brought to the emergency room with complaints of loss of orientation, confusion, inability to walk, refusal to eat and drink, rigidity in the body, visual hallucinations, and blood pressure fluctuations. His complaints started suddenly 3 days ago. He was receiving mirtazapine 30mg/day for depression. He also was receiving metoprolol 50mg/day and clopidogrel 75mg/day for coronary artery disease, for nearly 15 years without any complaints.

On psychiatric examination, the patient did not recognize his relatives and had fluctuating orientation and distractibility. On neurologic examination, consciousness was clear, pupils were isochoric, rigidity in both upper extremities in the form of lead tubular rigidity, mild rigidity in the left lower extremity, decreased amount of speech, and dysphonia. Nuchal rigidity was not observed. Deep tendon reflexes were normal. Body temperature was 37.1C, pulse rate ranged from 85-112, and respiratory rate 13-24 per minute. His Blood pressure ranged between 155/95-120/70.

Electrocardiogram showed no acute ischemic changes. In biochemistry measurements, CPK +2733 U/L (the highest value measured by the device, normal value [n] 39-308), C Reactive Protein 25 mg/L (n:0-5), Lactate Dehydrogenase +2086 U/L (n:1-248), Aspartate Aminotransferase 2461 U/L (n:1-50), Alanine Aminotransferase +1427 U/L (n:1-50), creatinine 2.01 mg/dL (n: 0.67-1.17), urea 110.6 mg/dL (n:17-43), glucose 66mg/dL(n:74-106), White Blood Cell count (WBC) 10.33 10^3/uL (n:4-10), Neutrophil count (Neu) 9.73 10^3/uL (n: 2-7), and myoglobinuria were detected. Cardiac troponin, electrolyte levels, autoimmune markers, and other blood values were normal. There was no acute ischemic change on cranial MRI. Brain CT showed no pathology.

The patient, who had no previous psychiatric admission, presented for the first time 7 months ago. The patient had complaints of anhedonia, loss of appetite, insomnia, low energy, and thoughts of worthlessness. Beck depression scale was applied and got 34 points. Depressive mood disorder was diagnosed according to DSM-V diagnostic criteria and mirtazapine 15mg/day was started. After 1.5 months, sleep problems partially improved other complaints persisted. Thereupon, mirtazapine was increased to 45mg/day. After 2 months, as his complaints regressed and his Beck depression scale score decreased to 13, mirtazapine was reduced to 30mg/day. After 2.5 months of regular treatment with mirtazapine 30mg/day, it was learned that the medication was discontinued

without medical advice, by the patient's caring family members who felt that the drug was no longer working, 20 days before the emergency presentation. Upon the onset of insomnia in the patient mirtazapine 30mg/day treatment was restarted 5 days before the emergency admission, by the patient's caring family members. His complaints started 2 days after the mirtazapine was restarted.

Diagnosed as atypical NMS according to Levenson's criteria (Levenson 1985). A possible causative agent, mirtazapine, was discontinued. The isoline-balanced electrolyte was started. Urine and blood cultures were collected. He was admitted to the Internal Care Unit. Bromocriptine 2.5mg 3*1 and lorazepam 1mg 2*1 were initiated via nasogastric tube. Urine alkalisation with sodium bicarbonate, hydration with %0.9 NaCl and supportive therapies were applied.

Urine and blood cultures showed no growth. Loss of orientation improved. Pulse, respiratory, and blood pressure irregularities are gone. Muscle rigidity disappeared. His body temperature did not rise above 37.0. No seizures or features were observed. Irregularities in biochemistry measurements improved day by day. At the end of the 10th day, biochemistry measurements CPK 185 U/L (n:39-308), WBC 9.3 10^3/uL (n:4-10), Neu 5.82 10^3/uL (n:2-7) and urine myoglobin was negative. With other biochemical blood parameters within the normal reference range and improvement of all symptoms, bromocriptine treatment was tapered and discontinued. His mood was euthymic. The patient was planned to be discharged for follow-up.

DISCUSSION

NMS is diagnosed if hyperthermia, muscle rigidity, elevated CPK, mental status change and autonomic instability are observed, according to DSM-V diagnostic criteria (DSM-V 2013). Atypical cases of NMS without hyperthermia and/or rigidity may therefore be missed (Szota et al. 2022). In this context, Levenson's NMS criteria can be used to avoid missing atypical NMS cases. In Levenson NMS criteria, fever, rigidity and increased CPK levels are major criteria, while tachycardia, abnormal blood pressure, tachypnea, diaphoresis, leukocytosis and altered consciousness are minor criteria. Diagnosis can be made with 3 major or 2 major and 4 minor manifestations (Levenson 1985). Our patient had rigidity, increased CPK level, tachycardia, abnormal blood pressure, tachypnea, leukocytosis and altered consciousness. Since 2 major and 5 minor Levenson criteria were fulfilled, atypical NMS was diagnosed.

NMS is a rare but potentially fatal complication, usually caused by antipsychotic drugs (Debeljak & Kores Plesničar 2021). The most suspected pathogenesis of NMS is decreased dopamine activity in the central nervous system associated with D2 dopamine receptor blockade, decreased dopamine release or dopamine depletion (Miranda et al. 2011, Reeves et al. 2001). Cases of NMS due to antidepressant use such as sertraline, venlafaxine and clomipramine have also been reported. (Miranda et al. 2011, Lu et al. 2006, Haddow et al. 2004).

NMS is often seen with the initiation or dose escalation of neuroleptic therapy. However, it may rarely occur with abrupt discontinuation of the drug. Rapid dose changes in medications, especially in the last 5 days before clinical onset, are a major risk factor for NMS. No significant association was found between the dose of the currently used drug or the duration of exposure and NMS (Chandran et al. 2003). In our case, despite being on medication for 6 months, NMS occurred when the medication was discontinued and the high dose was suddenly restarted.

Mirtazapine is an antidepressant agent with dual noradrenaline and specific serotonergic effects. Mirtazapine increases noradrenaline activity by blocking the alpha-2 receptor. Noradrenaline increases sympathetic nervous system activity. The sympathetic nervous system has strong effects on skeletal muscle work and the thermoregulation center. According to a study, dopamine decreased, noradrenaline increased and serotonin/dopamine ratio increased in acute NMS in platelet-poor plasma (Lu et al. 2006). Although NMS usually develops with dopamine antagonists, the autonomic dysfunction seen in NMS is largely due to adrenergic hyperactivity and dysregulation (Stevens 2008). Serotonin reduces the release of dopamine via the 5-HT2a receptor. Thus, it has been suggested that the EPS side effect occurs due to its inhibitory effect on extrapyramidal dopamine activity (Steele et al. 2011). Overstimulation of 5-HT2a receptors is thought to be the cause of Serotonin Syndrome (SS) (Debeljak & Kores Plesničar 2021). These suggest that both NMS and SS may have a common pathophysiology. Mirtazapine has been shown to release dopamine via 5-HT1A agonism (Nakayama et al. 2004). Thus, mirtazapine may both increase and decrease dopamine release. In the aforementioned case, there was a rapid starting of high-dose mirtazapine. Mirtazapine may have caused NMS by acting like a dopamine antagonist via the 5-HT2a receptor. Naranjo Adverse Drug Reaction (ADR) probability scale is a sensitive scale for Adverse Drug Reactions. According to the Naranjo ADR probability scale, a score of more than 9 means definite ADR, a score between 5-8 means probable ADR, a 1-4 score means possible ADR

and a 0 score means doubtful ADR. (Naranjo et al. 1981). In our case, mirtazapine scored 6 on the Naranjo probability scale. As a result of all these, it was thought that mirtazapine caused the development of atypical NMS in our patient. No case of NMS directly related to mirtazapine has been reported in the literature to the best of our knowledge.

Central nervous system infections, sepsis, subcortical structural lesions, autoimmunity, systemic diseases (pheochromocytoma, thyrotoxicosis, tetanus), serotonin syndrome, malignant hyperthermia (MH), intoxication (such as lithium, aspirin or heavy metal), central anticholinergic syndrome and lethal catatonia (LC) should be considered in the differential diagnosis. Central nervous system pathology was ruled out with Brain CT and Diffusion MRI. According to biochemical blood tests, sepsis, autoimmunity and other systemic diseases were ruled out.

NMS starts in days to weeks, whereas SS starts in minutes to hours. NMS takes around 10 days to resolve, whereas SS is shorter. In NMS, rigidity is more often seen in the upper extremities in the form of a lead pipe pattern, whereas in SS, increased muscle tone is more often seen in the lower extremities (Debeljak & Kores Plesničar 2021).

Increased CPK, altered mental status, tachycardia and diaphoresis are common findings in both NMS and LC. Insomnia and anxiety may be observed prodromal in LC. Psychosis, hyperactivity, agitation, and catatonic excitement may follow. While waxy flexibility, dystonia and stereotypic movements are more common in LC, lead-pipe rigidity is more suggestive of NMS (Desai et al. 2021, Szota et al. 2022). Insomnia in the case, which occurred a few days before the onset of complaints, was attributed to mirtazapine discontinuation and not to LC.

The central anticholinergic syndrome is differentiated from NMS by normal CPK levels and no rigidity. Mydriasis and photophobia may also occur in central anticholinergic syndrome (Szota et al. 2022)

Our patient had common clinical findings with both SS and MH. However, the fact that the patient was not exposed to inhaled anesthetic drugs and a nondepolarizing muscle relaxant has led us away from MH. The fact that the patient had no clonus, no diarrhea, normal deep tendon reflexes, and the onset of the clinic within days led us away from serotonin syndrome. The presence of rigidity, leukocytosis, altered consciousness, autonomic instability, elevated CK, acute renal failure, and rapid drug dose change within 5 days led us away from other diagnoses and towards the diagnosis of NMS. Hyperthermia was not observed in the patient and atypical NMS without hyperthermia has been reported (Szota et. al 2022).

CONCLUSION

The case of mirtazapine-induced NMS presented here shows that NMS may occur without all of the cardinal symptoms. Alternative NMS diagnostic criteria, such as the Levenson's diagnostic criteria may be uased to diagnose atypical cases early. Early diagnosis and treatment may reduce the mortality and morbidity of NMS complication. It should be kept in mind that the use of antidepressants may cause NMS, which is a rare side effect. Close follow-up in terms of NMS and other drug side effects is important in psychotropic drug changes or dose increases. In psychotropic drug changes, tapering off and starting the drug slowly may be effective in reducing the risk of developing NMS.

Ethical Considerations: Does this study include human subjects? YES

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Correspondence:
Talha Ağaç, MD, University of Health Sciences,
Bagcilar Training and Research Hospital,
Department of Psychiatry, 34200, Istanbul, Turkey.
talhaagac@hotmail.com, 0090 2124404000