CASE REPORT / OLGU SUNUMU

Delayed and Atypical Neuroleptic Malignant Syndrome Following Extended-Release Injectable Aripiprazole Use

Uzun Salınımlı Enjekte Edilebilir Aripripazol Kullanımını Takiben Gecikmiş Ve Atipik Nöroleptik Malign Sendrom

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ABSTRACT

Aim: Neuroleptic malignant syndrome (NMS) is an uncommon but life-threatening condition associated with antipsychotic medications that interfere with central dopaminergic pathways. While typically linked to high-potency antipsychotics like haloperidol, atypical antipsychotics such as aripiprazole can also induce NMS. The syndrome is characterized by hyperthermia, autonomic instability, altered mental status, and muscle rigidity, though atypical cases may lack some of these hallmark features. We aim to present an NMS case presented with delayed atypical symptoms following extended-release injectable (ERI) aripiprazole.

Case Presentation: A 40-year-old female patient with bipolar disorder and major depression arrived at the emergency department complaining of decreased mental clarity, difficulty with swallowing solid food, and impairments in communication and mobility who received ERI aripiprazole 40 days prior to admission. Despite lacking rigidity, she exhibited motor jerks, autonomic instability, and a delayed elevation in creatine kinase levels. NMS was diagnosed after excluding other causes, but the patient deteriorated rapidly, developing acute renal failure, cardiovascular instability, and malignant arrhythmia, which led to death.

Conclusion: This case highlights the potential for delayed and atypical presentations of NMS with ERI aripiprazole, emphasizing the need for clinicians to maintain a high index of suspicion for NMS, even when typical symptoms like rigidity are absent.

Keywords: Neuroleptic malignant syndrome, antipsychotic agents, aripiprazole

ÖZ

Amaç: Nöroleptik malign sendrom (NMS), santral dopaminerjik yolaklar üzerine etkili antipsikotik ilaçlarla ilişkili nadir görülen ancak yaşamı tehdit eden klinik bir durumdur. Genellikle haloperidol gibi yüksek etkili klasik antipsikotiklerle ilişkilendirilirken, aripiprazol gibi atipik antipsikotikler de NMS'ye neden olabilir. Sendrom, hipertermi, otonomik instabilite, değişen mental durum ve kas rijiditesi ile karakterizedir, ancak atipik vakalarda bu belirgin özelliklerden bazıları eksik olabilir. Uzun etkili enjektabl (USE) aripiprazol kullanımı sonrası gecikmiş atipik semptomlarla gelen bir NMS olgusunu sunmayı amaçladık.

Olgu Sunumu: Olgumuzda bipolar bozukluğu ve majör depresyonu olan ve uzun salınımlı enjektabl (USE) aripiprazolden sonra atipik NMS gelişen 40 yaşında bir kadın vakasını sunuyoruz. Rijiditesi olmamasına rağmen, motor atımlar, otonomik instabilite ve kreatin kinaz seviyelerinde gecikmeli yükselme meydana gelen hastada NMS, diğer nedenler dışlandıktan sonra teşhis edildi, ancak hastanın kliniği hızla kötüleşti; akut böbrek yetmezliği, kardiyovasküler instabilite ve malign aritmi hastanın ölümüyle sonuçlandı.

Sonuç: Bu vaka, USE aripiprazol kullanımı ile NMS'nin gecikmiş ve atipik semptomlarla başvurma potansiyelini vurgulayarak, rijidite gibi tipik semptomlar olmasa bile klinisyenlerin NMS'ye karşı yüksek bir şüphe barındırmaları gerektiğinin altını çizmektedir.

Anahtar Kelimeler: Nöroleptik malign sendrom, antipsikotikler, aripiprazol

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Introduction

With a 0.02% to 3.2% incidence rate, neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal condition linked to the use of antipsychotic medications that affect central dopaminergic neurotransmission. NMS can lead to a 10%-55% mortality rate (1). Dopamine antagonist exposure, altered mental status, rigidity, hyperthermia, and autonomic instability are typical diagnostic criteria for NMS. Other symptoms that may be present include diaphoresis, tachycardia, mutism, tachypnea, cardiovascular lability, and incontinence, with no apparent underlying neurological, metabolic, infectious, or other cause (2). We present a case of a patient who developed NMS in an atypical and delayed fashion following the administration of extended-release injectable aripiprazole.

Case Presentation

A 40-year-old female patient arrived at the emergency department complaining of decreased mental clarity, difficulty with swallowing solid food, and impairments in communication and mobility. Her medical history included hypothyroidism, hypertension, generalized anxiety disorder, and most recently, bipolar illness and major depression. Hence, she was prescribed lithium 1200 mg daily, venlafaxine 300 mg daily, bupropion 150 mg daily, and aripiprazole 200 mg monthly on a regular basis. Her oral aripiprazole 20 mg/day therapy was changed to 200 mg intramuscular extended-release aripiprazole 40 days prior to admission. The patient's next of kin informed our team that the patient's symptoms began following her second dose ten days ago, progressively deteriorated over time, and reached their peak within the past three days. She denied infectious symptoms, unusual food or drug intake, and random unprotected sexual intercourse. Initial vital signs were noted as; Glasgow Coma Scale Score 13/15 (E3V4E6), blood pressure 153/99 mmHg, pulse rate 103/bpm, temperature 36.8 °C, oxygen saturation 99%, respiratory rate 28/pm. On physical examination, the patient was disorganized, only responded with single words, and opened her eyes in response to verbal stimuli. There was no evidence of rigidity. With painful stimuli, all extremities had 4 points out of 5 on the muscle power scale. Upon admission, there were noticeable jerks in the left arm and right leg.

Her antipsychotic medications were discontinued, and intravenous hydration was started. According to her laboratory results, there was no evident pathology related to infection causes or electrolyte-metabolic abnormalities. Lithium blood level was within the therapeutic range. Serum creatinine kinase levels were the only laboratory parameter that changed noticeably. The measured blood creatinine kinase result was 284 U/L (with a reference cutoff of 145 U/L). Thoracic and abdominal computer tomography (CT) scans reported no evidence of an infection. Central imaging (non-contrast brain CT scan and diffusion-weighted magnetic resonance imaging) revealed no evidence of pathology. The electroencephalogram test showed intermittent slowing. Biperiden hydrochloride 10 mg was administered via IV route for suspected extrapyramidal adverse reaction resulting in automatic motor activity in the extremities. 10 mg of diazepam was administered via IV route to relieve the motor activity in the setting of a focal seizure to whom motor activity persisted following the biperiden hydrochloride.

Repeated laboratory tests resulted in creatinine: 2.2 mg/dl (initial 0.81 mg/dl), blood urea nitrogen (BUN): 32 mg/dl, K: 4.4 mEq/L, pH.7.24, base excess (BE): -5, HCO3: 22 mmol/L, lactate: 1.7, creatinine kinase : 483 U/L, no increase in the acute phase reactants. Intravenous hydration continued.

At the 30th hour of admission, 38.3°C and 38.5°C fever measurements were documented. In addition to applying a cold compress along with administering an intravenous dose of 1 gram of paracetamol, the patient also underwent repeat laboratory testing and blood cultures. Ceftriaxone for prophylaxis was initiated. No evidence of infection was present in the laboratory tests.

Contrast-enhanced brain magnetic resonance imaging (MRI) was performed to detect space-occupying lesions and central system infection due to the patient's state of somnolence and the development of nonsensical speech. 10 mg of intravenous midazolam was given before the MRI in order to minimize motor activity and provide sedation. The contrast-enhanced cranial MRI, which was obtained at 48th hours of admission revealed no signs in favor of intracranial mass or encephalitis.

At the 50th hour of admission, a fever of 38.3 °C was documented again. A lumbar puncture was performed.

Along with the recurrent motor activities on the extremities, the patient’s GCS score has deteriorated; consequently, she required an RSI with IV midazolam 0.15 mg/kg and IV 0.8 mg/kg rocuronium. As hypotension occurred and persisted, noradrenaline infusion was initiated with 0.1 mcg/kg/min dosing, titrated to 0.25 mcg/kg/min.

The cerebrospinal fluid (CSF) culture showed no signs of bacterial or fungal colonization, and the laboratory findings revealed the following: glucose 131 mg/dL (concurrent blood glucose level 201 mg/dL), protein 38 mg/dL, LDH 62 U/L, and Cl 141 meq/L. Peripheral blood cultures revealed gram (+) clustered cocci and gram (-) bacillus colonization. Although bacterial infection was not considered in the foreground, intravenous treatment with meropenem and vancomycin was initiated. As the following culture typing analysis resulted afterwards, gram (+) clustered cocci colonization was reported more likely as a contamination (coagulase [-] Staphylococcus spp.), and gram (-) bacillus colonization was reported as Acinetobacter lwoffii and Acinetobacter calcoaceticus, which are sensitive to meropenem.

The patient was transferred to the intensive care unit (ICU) at the 66th hour of ER admission. The patient's jerks continued upon admission to the intensive care unit, and their body temperature rose to 38°C. Control test results showed a substantial rise in CK (3556 U/L) and creatinine (3.64 mg/dL) which was accompanied by acidemia and anuria, therefore the patient was taken under dialysis. As the patient's need for vasopressors increased following hemodialysis, IV vasopressin was added with an infusion rate of 0.04 IU/min. Fever persisted during the ICU stay. Soon after, cardiovascular instability further led to malignant arrhythmia and eventually cardiac arrest. Written informed consent was obtained from the next of kin.

Discussion

NMS is a rare but potentially lethal complication of antipsychotic medications. Typical, high-potency antipsychotics such as haloperidol are among those most likely responsible; however, reports have linked a variety of drug classes, including low-potency and atypical antipsychotics, as well as antiemetic drugs that block dopaminergic receptors, to NMS (2,3).

Central dopaminergic receptor blockage is the pathogenic mechanism causing autonomic instability, hyperthermia, and parkinsonian symptoms such as rigidity (4). It is believed that central dopaminergic receptor inhibition at the hypothalamus results in hyperthermia and autonomic instability, whereas central receptor blockade in the nigrostriatal pathways causes parkinsonian-type symptoms such as rigidity (2,4). Aripiprazole is an atypical antipsychotic that acts as a partial agonist at the dopamine D2/D3/D4 receptors, in contrast to the antipsychotics that have stronger D2 blockage. It additionally features concurrent partial agonist action at serotonin 5-HT1A receptors and antagonist activity at 5-HT2A receptors (2,5).

There is no specific diagnostic test for NMS. A comprehensive history, physical examination, and laboratory results, such as increased creatine kinase (more than 1000 IU/L), can assist confirm the clinical diagnosis in individuals with suspected NMS (6). In a consensus study conducted in 2010 aiming to diagnose NMS using the Delphi method, diagnostic criteria were determined by the consensus of a committee consisting of 11 psychiatrists, 2 anesthesiologists, 2 emergency specialists, and 2 neurology specialists (Table 1) (7). A higher score is associated with the diagnosis, although the exact threshold number remains undetermined (7). The latest DSM-V criteria were also published a table of similar criteria for the diagnosis of NMS (8). Table 2 shows the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for NMS; including administration of a dopamine-blocking agent in the prior 72 hours, hyperthermia, rigidity, and altered level of consciousness (major criteria), and the presence of at least 2 of the following signs: tachycardia, diaphoresis, urinary incontinence, tachypnea, blood pressure fluctuations, elevated creatine kinase (CK) level, and leukocytosis, after exclusion of other causes (8). Leukocytosis with a left shift, electrolyte imbalances, elevated liver function tests, increased creatinine, and myoglobinuria due to rhabdomyolysis are other nonspecific laboratory findings (2).

The dosing and time frame between antipsychotic use and the onset of NMS is unique. Prior NMS history, high antipsychotic dosages, parenteral administration, recent or abrupt dose increases, switching antipsychotics, dehydration, and concurrent use of lithium, anticholinergic drugs, and antidepressants are risk factors for NMS (2).

Diagnostic criterion	Priority score*
Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours	20
Hyperthermia (>100.4°F or >38.0°C on at least 2 occasions, measured orally)	18
Rigidity	17
Mental status alteration (reduced or fluctuating level of consciousness)	13
Creatine kinase elevation (at least 4 times the upper limit of normal)	10
Sympathetic nervous system lability, defined as at least 2 of the following: • Blood pressure elevation (systolic or diastolic ≥25 percent above baseline) • Blood pressure fluctuation (≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 hours) • Diaphoresis • Urinary incontinence	10
Hypermetabolism, defined as heart-rate increase (≥25 percent above baseline) AND respiratory-rate increase (≥50 percent above baseline)	5
Negative work-up for infectious, toxic, metabolic, or neurologic causes	7

Table 1. Neuroleptic malignant syndrome diagnostic criteria: Expert panel consensus
No threshold score has been defined and validated for us in making a diagnosis of NMS.
* The mean priority score indexes each criterion according to its relative importance in making a diagnosis of NMS according to an expert panel.
Adapted from Gurrera et al. (7)

Diagnostic criteria of NMS based on DSM-V (9)	
Major symptoms	Rigidity Hyperthermia (>38.0°C, measured minimum 2 times orally) Diaphoresis Exposure to dopamine antagonist within 72 h prior to the beginning of symptoms
Minor symptoms	Autonomic nervous system: Tachycardia (rate > 25% above baseline), hypertonia (>25% above baseline or with fluctuation), sialorrhea, urinary incontinence, pallor, tachypnea (>50% above baseline), dyspnea Mental status: Altered consciousness: qualitative (delirium); quantitative (stupor to coma) Motor symptoms: Tremor, akinesia, dystonia, myoclonia, trismus, dysarthria, dysphagia Laboratory findings: ↑Leukocytes, ↑CK, ↑Myoglobin, ↑Catecholamines, ↑Creatinine, ↓Fe, metabolic acidosis, hypoxia
Exclusion criteria	The above-named symptoms are not due to another substance or a neurological or other general medical condition

Table 2. Diagnostic criteria of NMS based on DSM-V
NMS, Neuroleptic malignant syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders.

For our patient, the calculated Delphi score was 73. Although there is no specific reference test, it has been observed that a high score correlates with the diagnosis. According to DSM-V, although NMS can be diagnosed, the absence of rigidity and initial CK elevation may make diagnosis challenging. Although the literature suggests that rigidity is a major criterion for diagnosis, a study by Gurrera et al. reported that its sensitivity was measured as 69% (10). The atypical NMS phenotype was anticipated to present with increased nausea and vomiting, lower creatine kinase peaks, less autonomic instability, and hyperthermia, as well as less severe and shorter NMS episodes. However, in our patient, clinical signs were delayed (mental status change), rigidity was absent, cardiovascular lability and CK increase followed by rhabdomyolysis, which emerged on the 3rd day of admission and 13th day of first complaints. The literature and our case suggest that, even at the possibility of reduced specificity, the absence of one or more of the primary components of NMS shall be disregarded when making a diagnosis of NMS in atypical cases. Clinical strategies for managing NMS during its acute phase include identifying potential symptoms, excluding differential diagnoses, ceasing antipsychotic medication, and putting both pharmaceutical and non-pharmacological therapies into practice.

After performing the appropriate tests for the central nervous system and metabolic reasons, no abnormality was identified in our patient. Investigations such as brain imaging and lumbar puncture are used to exclude other causes for altered mental status such as neurological disease and infection. EEG showed slowed activity and excluded epileptic seizures. The patient had no suicidal ideation, side effects of his medications were monitored and there was no evidence of intoxication. Lithium levels were also monitored within the therapeutic range. Serotonin syndrome (associated with the use of serotonergic agents) was another differential in this case, but the patient did not exhibit autonomic features, such as hyperhidrosis and diarrhea, or muscular signs, such as hyperreflexia and myoclonus, which are typical of this syndrome. According to the blood culture typing results, which were reported 1 week after the sample was taken, Acinetobacter lwoffii and A. calcoaceticus growth were detected in the blood. Although there was no risk factor for opportunistic infection in the patient, it is still unknown whether this situation is due to colonization or infection. Although acinetobacter species growth in the blood culture may be the cause of persistent fever and other symptoms, since the patient's reason for application was progressively increasing central symptoms for the last 10 days and there was no growth in the CSF culture, it was thought that the cause of the symptoms would not be primarily bloodstream infection. However, as soon as the culture result was obtained, the patient was started on meropenem without waiting for the typing. The susceptibility to meropenem of A. lwoffii and A. calcoaceticus was confirmed after all.

Frequent monitoring and supportive care are necessary to prevent complications such as acute renal failure, acute respiratory failure, arrhythmias, myocardial infarction, seizures, and sepsis. It is essential to administer intravenous fluids to maintain a euvolemic state and to prevent fever (2). Pharmacological interventions aim to reduce muscle rigidity, reverse the dopaminergic blockade, and control agitation or behavioral disturbance, which can be component of the underlying psychiatric disorder or a response to the NMS itself (3).

Dantrolene (1-2.5 mg/kg intravenously, up to 10 mg/kg/day), a direct-acting skeletal muscle relaxant, is often used in adults with NMS and has been reported to decrease rigidity and hyperthermia. When used at large doses, there is an elevated risk of hepatotoxicity (2).

It is also possible to use amantadine, a weak, noncompetitive N-methyl-D-aspartate receptor antagonist (100 mg orally to a maximum of 200 mg every 12 hours), and bromocriptine, a D2 agonist (2.5 mg through nasogastric tube every 6-8 hours, up to 40 mg/day). Benzodiazepines have been demonstrated to reduce mortality and are useful in providing muscle relaxation and managing agitation or behavioral disturbance (11).

Dantrolene sodium could not be administered to the patient because it was not available in the emergency department and, therefore administered in the intensive care unit. We believe that the diagnosis is strengthened by the fact that the patient's symptoms improved as benzodiazepines were administered, and that during follow-ups in intensive care, CK levels were higher than 3000 U/L.

Conclusion

This case is an example of NMS with atypical and delayed signs, associated with ERI aripiprazole. We should emphasize that NMS may develop as a complication of aripiprazole ERI formulations.

The delayed onset and the absence of major symptoms of NMS in our patient are atypical features that complicate the management. Therefore, clinicians should be aware that NMS is heterogeneous in onset, presentation, and progression.

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Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review in this journal.

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