Turk J Intensive Care 2021;19:94-97
DOI: 10.4274/tybd.galenos.2021.18480

CASE REPORT / *OLGU SUNUMU*

İrem Akın Şen,
Metin Kılınç,
Cem Şen,
Hülya Sungurtekin

Neuroleptic Malignant Syndrome Requires Intensive Care Monitoring: A Review with Three Cases

Yoğun Bakımda Takibi Gerektiren Üç Nöroleptik Malign Sendrom Olgusu ve Literatür Taraması

Received/Geliş Tarihi : 21.12.2020
Accepted/Kabul Tarihi : 01.02.2021

İrem Akın Şen, Metin Kılınç, Hülya Sungurtekin
Pamukkale University Faculty of Medicine, Department of Anesthesiology and Reanimation, Intensive Care Unit, Denizli, Turkey

Cem Şen
Servergazi State Hospital, Clinic of Emergency Medicine, Denizli, Turkey

İrem Akın Şen MD, (✉),
Pamukkale University Faculty of Medicine, Department of Anesthesiology and Reanimation, Intensive Care Unit, Denizli, Turkey

E-mail : driremakinsen@hotmail.com
Phone : +90 505 626 05 18
ORCID ID : orcid.org/0000-0002-5402-4636

ABSTRACT Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic and potentially fatal side effect of antipsychotics. The syndrome is characterised by hyperthermia (fever), muscle rigidity, autonomic disturbances and alterations of mental state. Psychotropic medications, such as typical and atypical antipsychotics, certain dopamine receptor-blocking drugs used in the treatment of nausea and gastroparesis (e.g. promethazine, metoclopramide and prochlorperazine) and antidepressants, such as amoxapine, have all been implicated in the aetiology of NMS. Herein, we report three cases of NMS and discuss their possible aetiology with reference to the existing literature.
Keywords: Fever, antipsychotics, mental state alterations

ÖZ Nöroleptik malign sendrom (NMS), antipsikotik ilaçların nadir görülen, idiyosenkratik, potansiyel olarak ölümcül bir yan etkisidir. Sendrom, hipertermi (ateş), rijidite, otonomik bozukluklar ve zihinsel değişiklikler ile karakterizedir. Tipik ve atipik antipsikotikler gibi psikotropik ilaçlar, bulantı ve gastroparezi tedavisinde kullanılan bazı dopamin reseptör antagonisti ilaçlar (örneğin; prometazin, metoklopramid, proklorperazin) ve amoksapin gibi antidepresanların tümü NMS etiyolojisinde yer almıştır. Bu olgu serisinde üç NMS olgusu bildirdik ve mevcut literatürler eşliğinde olası etiyolojileri tartışmayı amaçladık.
Anahtar Kelimeler: Ateş, antipsikotikler, mental durum değişikliği

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic and potentially fatal side effect of antipsychotic medications (1). First described in 1968 (2,3), shortly after the introduction of neuroleptics, it occurs in about 0.2% of patients (4) treated with the medications. The prevalence of NMS is found to be variable, ranging from 0.02 to 2.4% (1). Syndrome is characterized by hyperthermia (fever), muscle rigidity, autonomic disturbances and mental state alterations.

Psychotropic medications such as the typical and atypical (5,6) antipsychotics, certain dopamine receptor-blocking drugs used in the treatment of nausea and gastroparesis (e.g., promethazine, metoclopramide, prochlorperazine), and antidepressants like amoxapine have all been implicated in the aetiology of NMS (7). Another precipitant is the abrupt discontinuation of anti-Parkinsonian agents (8). Some cases have been reported after the use of cocaine (5) and lysergic acid diethylamide (9). Despite being a well-recognised condition, the pathogenesis of NMS is not fully understood. Although many risk factors have been identified, predicting which patients will develop NMS and when, remains extremely difficult (10). We report three cases of NMS and discuss possible etiologies with reference to the existing literature.

Case Reports

Two of the three patients were male and one were female. None of the patients had a previous diagnosis of NMS. All patients had a previously known psychiatric disorder. Two of the patients were using a combination of typical and atypical antipsychotics and the other was using lithium and antipsychotics. All patients had high fever and blurred consciousness, but rigidity was not seen in any patient. Creatine kinase (CK) was elevated in all patients. One of the patients died during the follow-up. Necessary consents were obtained from all patients.

Case 1

A seventy-one-year-old male patient was brought to the emergency department by his relatives due to blurred consciousness, unresponsiveness, and speech impairment. Patient was started risperidone, quetiapine and sodium valproate five days ago. Three days after started the medications, his complaints have appeared. In physical examination; Glasgow coma score (GCS): $E_1M_4V_3$, blood pressure: 128/77 mmHg, heart rate: 103/min, saturation: 96%, respiratory rate: 23/min, no rigidity. The patient had fever of 38.9 °C and white blood cell (WBC) count: 10,140/mm^3, and CK: 3,026 U/L were detected in the laboratory. Patient was admitted to intensive care unit with a preliminary diagnosis of NMS. Patient was consulted to the neurology and psychiatry. Only hydration was recommended. Patient's general condition gradually deteriorated during follow-up and was intubated on the fifth day of hospitalization. The patient died on the 8th day of hospitalization.

Case 2

A nineteen-year-old female patient were following up with congenital mental developmental delay and psychotic disorder for 10 years. She was brought to the emergency department by her relatives due to blurred consciousness, tremors and fever. It was learned that, due to the deterioration in oral intake during the last ten days; she has not been used the medication; quetiapine, clonazepam and biperiden. In physical examination; GCS: $E_4M_3V_1$, blood pressure: 98/63 mmHg, heart rate: 82/min, saturation: 94%, respiratory rate: 12/min, no rigidity. The patient had fever of 38.5 °C and WBC: 10,000/mm^3, and CK: 3,803 U/L were detected in the laboratory. Patient was admitted to intensive care unit with a preliminary diagnosis of NMS. Patient was consulted to the neurology and psychiatry. Hydration and supportive treatment recommended. CK decreased to 300 U/L and vitals were stable, he was transferred to the neurology department. The patient was hospitalized for 15 days. He was discharged on 25th day.

Case 3

Sixty-one years old male patient were using risperidone, lithium and quetiapine for psychosis. He was brought to the emergency department by his relatives due to deterioration in his communication with relatives, inability to sleep, confusion and fever. It was learned from the relatives that the patient voluntarily discontinued his medication. In physical examination; GCS: $E_2M_4V_3$, blood pressure: 118/69 mmHg, heart rate: 77/min, saturation: 100%, respiratory rate: 15/min, no rigidity. The patient had fever of 39,2 °C and WBC: 6,720/mm^3, and CK: 4,545 U/L were detected in the laboratory. The patient was hospitalized with a pre-diagnosis of NMS. Hydration and supportive treatment was started. The patient's CK value regressed to normal limits. The patient treatment was regulated and discharged with recommendations.

Discussion

NMS is a rare clinical entity characterized by mental status change, motor abnormalities such as, rigidity and bradykinesia, autonomic dysfunction (such as blood pressure changes, diaphoresis and tachycardia) and fever. Although rare, it can lead to life-threatening complications that require immediate intervention. Laboratory findings such as leukocytosis, CK and elevation in liver function tests frequently accompany the clinical picture (6,11-14). Clinical findings of NMS include; changes in consciousness, hyperthermia, diaphoresis, elevated or labile blood pressure, dysphagia, incontinence, lead-tube rigidity, akinesia or dystonia, rhabdomyolysis, myoclonus. Not all NMS findings may be present at the same time (15). None of our cases had rigidity. Leukocytosis and CK elevation were observed in all of our cases. We lost one of our patients despite all the treatments.

Normal oral temperature of a man is 35.7-37.7 degrees (96.3-99.9 °F). Hyperpyrexia (temperature above 38 °C) was encountered in almost all cases. All of our patients had fever.

Central dopaminergic hypoactivity due to sudden discontinuation of dopaminergic agents or antipsychotics, or the use of dopamine antagonists is the main cause of NMS (6,13-16). Although NMS is mostly associated with the use of typical and high potency antipsychotics (such as

haloperidol), there are also cases identified with other low potency antipsychotics and new atypical antipsychotics (17). Few cases have been reported either due to the use of lithium and other antipsychotics or due to the combination of anticonvulsants such as carbamazepine and tricyclic antidepressants (18,19). All of our cases had a history of antipsychotic use. The most frequently encountered drugs in our patients were risperidone, an atypical antipsychotic, and quetiapine, a combination of other antipsychotics.

The main predisposing factors to facilitate the development of NMS include male sex, young age, dehydration, hyponatremia, agitation, intramuscular or parenteral administration of antipsychotic medication, or use of depot formulas, high dose neuroleptic uptake and rapid dose titration, concomitant use of lithium and reuptake inhibitors, mental retardation, extrapyramidal syndromes, psychomotor agitation, malnutrition, emotional stress, infections and previous history of NMS (6,12,14,16,20,21). Two of our cases were male and one was female. One of our patients did not take their medication due to oral intake disorder and the other was stopped because of their own will; it was thought NMS might have developed.

Laboratory changes that we frequently see in NMS include; increased serum CK level (>1,000 IU/L), elevation in liver, kidney and coagulation tests, leukocytosis, electrolyte changes, proteinuria and rhabdomyolysis (16). All of our patients had a high CK value and decreased to normal limits after treatment. Rhabdomyolysis is one of the major complications that may occur during the course of NMS. Increased CK value with deterioration of renal function and darkening of urine color but no hematuria detected on urine microscopy should be a warning for rhabdomyolysis. No pathology related to liver or kidney was detected in any of our patients. Rhabdomyolysis was not seen in any our patients.

Discontinuation of the medicatio is the most important step in the treatment. Dehydration, electrolyte imbalance, protection from infection and thrombosis, supportive therapies for hyperthermia and acute renal failure are important in reducing morbidity and mortality (20). Dopaminergic agents such as bromocriptine and amantadine, dantrolene, and lorazepam and diazepam which are effective over the GABA'ergic system are the most commonly used pharmacological treatment methods. Drug therapy should be continued for at least two to three weeks until symptoms disappear and are completely healed (20,22). If the use of antipsychotic medication is to be initiated after complete treatment of NMS, it should be performed at low doses, by slow titration, avoiding dehydration and the use of lithium together (14,16).

As a result, NMS is a serious and life-threatening condition. Early diagnosis and appropriate treatment are of great importance in reducing mortality and morbidity. Although NMS is a psychiatric diagnosis, its treatment requires a very complicated and systematic approach. In this regard, after any neuroleptic intake, patients with suspicious symptoms and signs should be carefully monitored and the most appropriate treatment should be given at the right time.

Ethics

Informed Consent: Necessary consents were obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.A.Ş., Design: İ.A.Ş., Data Collection or Processing: İ.A.Ş., Analysis or Interpretation: İ.A.Ş., M.K., C.Ş., H.S., Literature Search: İ.A.Ş., M.K., C.Ş., H.S., Writing: İ.A.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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