Case Report

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Management of a trauma patient with alcohol withdrawal who developed neuroleptic malignant syndrome in Korea: a case report

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Neuroleptic malignant syndrome (NMS) is a rare but fatal condition, with a high mortality rate. NMS is characterized by altered mental status, fever, myoclonus, autonomic dysfunctions, and elevated creatinine phosphokinase. The clinical manifestations may be confused with alcohol-related symptoms, trauma, sepsis, postoperative agitation, or malignant hyperthermia. A 69-year-old male patient with alcohol withdrawal was admitted to the operating theatre to rule out septic shock due to mesenteric injury after multiple trauma. He was suspected NMS with abrupt increase body temperature to 41.7°C after haloperidol administration. Active cooling and rapid fluid infusion was done during anesthesia. Delayed diagnosis and treatment of NMS lead to catastrophic result. Therefore, if the patient's past medical history is unknown or clinical symptoms develop that are suggestive of NMS, early treatment must be considered.

Keywords: Alcohol withdrawal delirium; Neuroleptic malignant syndrome; Wounds and injuries; Case reports

INTRODUCTION

Neuroleptic malignant syndrome (NMS) may be confused with several medical conditions that occur during the perioperative period and may be overlooked. NMS is characterized by altered mental status, fever, myoclonus, autonomic dysfunctions, and elevated creatinine phosphokinase (CK) [1]. NMS is an uncommon condition, with an incidence of 0.01% to 3% in patients taking neuroleptic agents. However, the mortality is as high as 5% to 20% [2]. The mechanism of NMS has not been clearly elucidated. One explanation is that the blockage of central dopamine receptors in the hypothalamus causes symptoms related to dysautonomia, including hyperthermia [3]. Blocking of the nigrostriatal dopamine pathways induces rigidity or tremor [3].

Haloperidol is a first-generation antipsychotic drug that is frequently used to prevent and treat postoperative delirium [4]. Haloperidol is also used to treat agitation caused by alcohol abuse [5]. Importantly, the use of antipsychotic agents to treat delirium

or agitation can cause NMS [6].

Here, we describe the management of a patient with alcohol withdrawal who had trauma surgery under general anesthesia and developed NMS after haloperidol use, along with a literature review.

CASE REPORT

A 69-year-old male patient (170 cm, 76 kg) was placed in the operating room for an emergency laparotomy. The patient had been on medication for diabetes and hypertension. He has also been medicated for major depressive disorder for 20 years but did not remember the name of his medication. Six years ago, the patient had a history of cranioplasty due to a fall during a suicide attempt. He was recently admitted to a psychiatric hospital for the treatment of alcoholism. The patient had been drinking almost every day for 30 years. At that hospital, the patient was given lorazepam. On the day of the transfer to Gachon University Gil Medical Center (Incheon, Korea), the patient was given lorazepam and haloperidol as he was irritable and aggressive. He was transferred to our hospital, a level I trauma center, following trauma due to the patient breaking a window of the first-floor ward and jumping out. The patient had multiple rib fractures without dyspnea, and hemoperitoneum was suspected. Diagnostic laparoscopy was performed in the operating room under general anesthesia to differentiate the intraabdominal damage. Bleeding control of the mesenteric injuries was conducted. The patient's vital signs were stable, and he was admitted to the general ward after surgery. The patient's systolic blood pressure was relatively stable at 120 to 130 mmHg, heart rate was 110 to 120 beats/min, body temperature was 36.5 °C, and oxygen saturation (SpO_2) was 95% to 98%. The patient's CK level was 515 U/L. On postoperative day 1, the patient was irritable. His SpO_2 intermittently decreased to 80%–90%. His body temperature was 37.4 to 37.7 °C. Hence, the patient was provided with oxygen 5 to 8 L/min via a facial mask. Lorazepam and haloperidol were administered. Subsequently, the patient's consciousness was lowered, and his vital signs were as follows: blood pressure of 133/60 mmHg, heart rate of 168 beats/min, and SpO_2 of 83%, despite oxygen supply with tachypnea. The patient's body temperature abruptly increased to 41.5 °C and he was sweating. The patient was transferred to the intensive care unit, and tracheal intubation was performed after using midazolam and vecuronium. To exclude the septic shock due to his intraabdominal injury, an emergency laparotomy was performed. In the operating room, the patient's vital signs measured as follows: blood pressure of 115/59 mmHg, heart rate of 163 beats/min, SpO_2 of 96%, and body temperature of 41.7 °C. He was sweating excessively. The color of his urine was dark. In the operating room, midazolam 2 mg and rocuronium 50 mg were administered after standard anesthetic monitoring, and controlled ventilation was initiated. Central catheterization was performed in the right internal jugular vein, and a radial arterial line was inserted. Arterial blood gas analysis revealed a pH of 7.34, $PaCO_2$ of 36 mmHg, and PaO_2 of 72 mmHg in fraction of inspired oxygen (FIO_2) of 0.8, K^+ of 5.2 mmol/L, and hematocrit of 35%. Cooling was initiated with a cold blanket, and normal saline and 6% hydroxyethyl starch were administered at a rapid rate. Anesthesia was maintained with sevoflurane (0.3–1.0 vol%) for a target bispectral index of 50 to 60. No intraabdominal lesions were detected during surgery. At the end of the 45-minute operation, the patient's vital signs were as follows: blood pressure of 120/46 mmHg, heart rate of 115 beats/min, SpO_2 of 100%, and esophageal temperature of 37.7 °C. The arterial blood gas analysis indicated a pH of 7.33, $PaCO_2$ of 36 mmHg, PaO_2 of 153 mmHg in FIO_2 of 0.8, K^+ of 3.4 mmol/L, and hematocrit of 24%. The total infused fluid volume was 1,800 mL, and the urine output was 140 mL. There were no specific findings on brain or abdominal computed tomography. The immediate postoperative CK was 2,004 U/L, and the white blood cell count was 17,130/mm^3. The patient was alert the next day. His systolic blood pressure was maintained at 110 to 150 mmHg. His heart rate was 90 to 110 beats/min. His body temperature was 37.5 to 37.8 °C. His SpO_2 was 96% to 100%. As the vital signs were stable, the patient was extubated. Thyroid function tests, including T3, free T4, and thyroid-stimulating hormone, were normal. The patient's condition remained stable during his hospital stay. He was transferred to a psychiatric hospital on postoperative day 4.

Ethics statement

The study was approved by the Institutional Review Board of Gachon University Gil Medical Center (No. GCIRB2022-130). The requirement for informed consent was waived because this was a retrospective review conducted using medical records.

DISCUSSION

In this case, although the patient has some complex situations that can be confusing with alcohol withdrawal, sepsis, injury for trauma, and postoperative delirium, there were clear findings suggestive of NMS. Despite symptoms such as confuse mentality, decreased oxygen saturation, tachycardia, fever, and increased CK level might appear in all of the above-mentioned situations,

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an abrupt and extreme high fever after use of neuroleptic drug strongly suggest NMS. Also, proper imaging studies, surgical observations, and laboratory test helped to rule out other diagnoses that could be confused with NMS and provided a basis for convincing that it was NMS.

Alcohol withdrawal mimics NMS with characteristic hyperadrenergic responses, altered mentality, rigidity, and elevated CK [7]. However, the mechanism is distinct from that of NMS. Chronic alcoholism causes downregulation of the γ-aminobutyric acid receptors and upregulation of the N-nitrosodimethylamine receptors with increased glutamate production [8]. When alcohol intake is abruptly reduced, hyperadrenergic responses occurred, as the changes from these activities are unmasked and glutamate-mediated central nervous system excitation increases [8]. The conjugation of haloperidol and benzodiazepine is commonly prescribed for alcohol-related agitations [5]. In our patient, a combination of lorazepam and haloperidol was administered to control agitation in both the psychiatric hospital and our trauma center, leading to NMS.

Treatment of NMS begins with the discontinuation of the causative agent, followed by supportive care [5]. Supportive care consists mainly of cooling to improve hypothermia and hydration to prevent renal injury due to rhabdomyolysis [9]. Bromocriptine, a dopamine D2 receptor agonist, and dantrolene, a muscle relaxant, are useful medical treatment options [10]. In particular, dantrolene is used in emergencies during general anesthesia. It is a familiar drug that is used with caution by anesthesiologists because it causes malignant hyperthermia (MH). MH is characterized by a rapid increase in body temperature, abrupt increase of the end-tidal carbon dioxide concentration, tachycardia, hyperkalemia, and elevated CK. MH is an autosomal dominant disease triggered by inhalation anesthetics or depolarizing neuromuscular blocking agents [11]. If the patient in this case developed the above symptoms during anesthesia, most anesthesiologists would suspect MH rather than NMS, and would not hesitate to use dantrolene. In this case, the patient had no specific event during the previous surgery and no family history of MH. His symptoms aggravated after the administration of haloperidol in the ward. As a result, MH was excluded. Moreover, the patient's response to cooling was good, and the end-tidal carbon dioxide concentration was within normal limits. The body temperature was corrected quickly, and tachycardia was corrected smoothly and in line with volume replacement. Therefore, for our patient, the use of additional dantrolene was not considered.

The use of dantrolene in NMS is controversial. Treatment with dantrolene and other drug combinations may delay clinical recovery. Moreover, dantrolene monotherapy increases the mortality risk [12]. Therefore, dantrolene should not be used for the routine management of NMS, although it should be considered as a treatment option if NMS arises.

The risk of NMS is increased in patients using selective serotonin reuptake inhibitors. This is because serotonin inhibits dopamine release and enhances the hypodopaminergic status induced by antipsychotics [13]. In this case, although the exact drug is unknown, the patient had been taking an antidepressant for a long time. It is known that tricyclic antidepressants can also cause NMS. As such, for patients with a history of antidepressant medications, there is a risk of NMS [14].

When looking after patients who are confused, such as our patient, the patient's underlying and/or chronic diseases or drug history may not be accurately provided to the clinicians. Head injury or sepsis may show similar symptoms to NMS. Therefore, these should be considered and excluded [10].

NMS was a rare clinical situation. Traditionally, the mortality rate of NMS was more than 25% [15]. Although the mortality rate has recently improved, it remains relatively high [15]. Early detection and timely active treatment can lead to full recovery within 2 to 14 days. In contrast, delayed recognition of NMS may lead to severe renal and cardiovascular morbidity and mortality [15].

In conclusion, NMS and alcohol withdrawal symptoms or postoperative agitation have similar clinical presentations. This similarity may delay the diagnosis and treatment of NMS. Additionally, traumatic symptoms may mask the manifestations of NMS. Therefore, if the patient's past medical history is unknown or clinical symptoms develop that are suggestive of NMS such as extreme high fever after exposure to dopaminergic blocking agent, muscle rigidity, altered mentality, autonomic irritability, excessive increase in CK level, early treatment must be considered.

ARTICLE INFORMATION

Author contributions

Conceptualization: all authors; Data curation: YYJ; Methodology: all authors; Project administration: all authors; Visualization: YYJ; Writing–original draft: BY, JYL, YYJ; Writing–review & editing: YBK, HYP, JJ, YYJ. All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Data availability
Data sharing is not applicable as no new data were created or analyzed in this study.

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