Delayed Onset of Suspected Malignant Hyperthermia During Sevoflurane Anesthesia in an Afghan Trauma Patient: A Case Report

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Malignant hyperthermia (MH) is a rare pathologic hypermetabolic pharmacogenetic disorder of skeletal muscle calcium regulation following exposure to depolarizing muscle relaxants and/or volatile anesthetics. Although its pathogenesis is relatively well understood, there is wide variability in both the time of onset and the presentation of clinical signs and symptoms. In some circumstances the delayed onset of the hypermetabolic state may hinder timely recognition and treatment. Differential diagnosis of an MH crisis can be particularly challenging in a trauma patient, especially in an austere environment. This case report describes the presentation and management of a suspected case of MH in an Afghan national who underwent surgery following lower extremity trauma resulting from an improvised explosive device.

Keywords: Emergency surgery, malignant hyperthermia, sevoflurane, succinylcholine, trauma.
### Table. Vital Signs and Laboratory Results

<table>
<thead>
<tr>
<th>Time</th>
<th>pH/Pco2 (mm Hg)/Po2 (mm Hg)/BE/Hco3 (mmol/L)</th>
<th>Serum potassium (mmol/L)</th>
<th>BP (mm Hg)</th>
<th>HR (/min)</th>
<th>Temperature, °C (°F)</th>
<th>MV (L/min)</th>
<th>Ventilation</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>7.34/48/25/0/26b</td>
<td>4</td>
<td>105/79</td>
<td>88</td>
<td>37.0 (98.6)</td>
<td>8.3</td>
<td>SV</td>
<td>Hb and Hct = 14.3 g/L and 42%</td>
</tr>
<tr>
<td>Intubation</td>
<td>ETCO2 = 42 mm Hg</td>
<td>110/72</td>
<td>90</td>
<td>37.0 (98.6)</td>
<td></td>
<td>CMV</td>
<td>Induction: midazolam 3 mg, fentanyl 200 μg, ketamine 50 mg, etomidate 30 mg, succinylcholine 120 mg</td>
<td></td>
</tr>
<tr>
<td>37 min</td>
<td>ETCO2 = 45 mm Hg</td>
<td>110/52</td>
<td>95</td>
<td>37.1 (98.7)</td>
<td>10.8</td>
<td>CMV</td>
<td>Surgery starts</td>
<td></td>
</tr>
<tr>
<td>73 min</td>
<td>7.26/51/217/−4/23</td>
<td>4.7</td>
<td>110/58</td>
<td>99</td>
<td>37.4 (99.2)</td>
<td>11.2</td>
<td>CMV</td>
<td>Hb and Hct = 11.2 g/dL and 33%; 4 U packed RBCs transfused</td>
</tr>
<tr>
<td>95 min</td>
<td>ETCO2 = 58 mm Hg</td>
<td>110/70</td>
<td>100</td>
<td>37.4 (99.2)</td>
<td>7.7</td>
<td>SV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>165 min</td>
<td>ETCO2 = 65 mm Hg</td>
<td>118/42</td>
<td>106</td>
<td>38.0 (100.4)</td>
<td>12.4</td>
<td>SV</td>
<td>Surgery ends. Sevoflurane off. Total opioids/ketamine = fentanyl 500 μg + morphine 25 mg + ketamine 100 mg, Hydromorphone 1.6 mg titrated.</td>
<td></td>
</tr>
<tr>
<td>178 min</td>
<td>ETCO2 = 90 mm Hg</td>
<td>140/78</td>
<td>110</td>
<td>38.1 (100.6)</td>
<td>4.8</td>
<td>SV</td>
<td>MMR/abdominal muscle rigidity noted</td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>7.16/65/42/−6/23b</td>
<td>5.5</td>
<td>140/80</td>
<td>110</td>
<td>38.1 (100.6)</td>
<td>30</td>
<td>CMV</td>
<td>Hyperventilation; albuterol 4 puffs + insulin 10 U + 25 g dextrose for hyperkalemia</td>
</tr>
<tr>
<td>185 min</td>
<td>ETCO2 = 67 mm Hg</td>
<td>120/60</td>
<td>112</td>
<td>38.3 (100.9)</td>
<td>10.8</td>
<td>CMV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>204 min</td>
<td>7.16/66/337/−5/24</td>
<td>6.1</td>
<td>168/70</td>
<td>115</td>
<td>38.3 (100.8)</td>
<td>18</td>
<td>CMV</td>
<td>Insulin 10 U + 25 g dextrose for hyperkalemia</td>
</tr>
<tr>
<td>215 min</td>
<td>ETCO2 = 62 mm Hg</td>
<td>162/90</td>
<td>118</td>
<td>38.3 (100.8)</td>
<td>18</td>
<td>CMV</td>
<td>Dantrolene 180 mg</td>
<td></td>
</tr>
<tr>
<td>235 min</td>
<td>ETCO2 = 34 mm Hg</td>
<td>142/62</td>
<td>85</td>
<td>38.1 (100.5)</td>
<td>18</td>
<td>CMV</td>
<td>MMR/muscle rigidity resolved</td>
<td></td>
</tr>
<tr>
<td>295 min</td>
<td>7.39/36/402/−4/21</td>
<td>5.4</td>
<td>128/62</td>
<td>80</td>
<td>38.1 (100.5)</td>
<td>12</td>
<td>CMV</td>
<td>CK = 918 U/L; Total crystalloids = 3.5 L, urine output = 700 mL, estimated blood loss = 250 mL</td>
</tr>
<tr>
<td>310 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transported to NATO hospital</td>
</tr>
</tbody>
</table>

Abbreviations: BE, base excess; BP, blood pressure; CK, creatine kinase; CMV, continuous mechanical ventilation; ETCO2, end-tidal carbon dioxide; Hb and Hct, hemoglobin and hematocrit; HCO3, bicarbonate; HR, heart rate; MMR, masseter muscle rigidity; MV, minute ventilation; NATO, North Atlantic Treaty Organization; RBCs, red blood cells; SV, spontaneous ventilation.

a Minutes since induction.
b Venous blood gas.
Hg; and temperature, 37.0°C (98.6°F). Oxygen was administered at 2 L/min, and the patient was mechanically ventilated with a tidal volume of 540 mL, respiratory rate of 15/min, and positive end-expiratory pressure of 5 cm H2O, with peak airway pressures of 18 cm H2O. All fluids were administered through a fluid warmer, and an upper-body warming blanket was placed at a temperature of 43°C. General anesthesia was maintained with 2% to 2.5% sevoflurane, rocuronium, fentanyl, morphine, and ketamine (see Table). Shortly after induction the tourniquet was removed from the left lower extremity. No tourniquet was used during the case.

Total operative time was approximately 2 hours, and during this period the patient received a total of 500 μg of fentanyl, 25 mg of morphine, and 50 mg of ketamine. The patient received a total of 3,500 mL of normal saline and 4 U of packed red blood cells and had 700 mL of urine output and 250 mL of estimated blood loss. At the conclusion of the surgery, the patient was spontaneously breathing at a rate of 20/min with a tidal volume of 620 mL and fraction of inspired oxygen (FiO2) of 0.86. He had a blood pressure of 118/42 mm Hg, heart rate of 106/min, temperature of 38.0°C (100.4°F), SaO2 of 100%, and an ETCO2 of 65 mm Hg. The end-tidal sevoflurane concentration was 1%. Train-of-four was 4/4 with sustained tetanus. Hydromorphone, 1.6 mg, was titrated because of suspected pain given the increased heart rate and respiratory rate. Fifteen minutes later the respiratory rate decreased to 4/min with a tidal volume of 1,200 mL, and an ETCO2 of 90 mm Hg. Blood pressure increased to 140/78 mm Hg, heart rate to 110/min, and SaO2 to 99%, and temperature had climbed to 38.1°C (100.6°F).

At this time it was determined that the hypercarbia was excessive given that the minute ventilation was approximately 5 L/min in a 70-kg man. Inspection of the anesthesia machine and breathing circuit ruled out any obvious equipment malfunction or carbon dioxide canister depletion. It was also noted at this time that the patient was exhibiting intense bilateral masseter muscle rigidity and increased rigidity of the abdominal musculature. No shivering or patient movement was noted. The temperature was now 38.3°C (100.9°F). Manual hyperventilation was initiated at high flows of oxygen, and several minutes later, the ETCO2 had decreased to 35 to 40 mm Hg. The patient was then returned to mechanical ventilation with a tidal volume of 900 mL and respiratory rate of 20/min. However, the ETCO2 increased to 67 mm Hg. Inspection of the Foley catheter revealed clear yellow urine. A venous blood gas finding confirmed the hypercarbia (ETCO2 = 66 mm Hg) and mild hyperkalemia (see Table). The hyperkalemia was treated with albuterol (4 puffs) via the endotracheal tube, 10 U of regular insulin, and 25 g of 50% glucose IV. Given the clinical picture, a diagnosis of suspected MH was made, and the patient was given dantrolene, 2.5 mg/kg (180 mg).

Following the completion of a dantrolene bolus, the patient displayed a gradual decrease in ETCO2 and resolution of the muscular rigidity. Twenty minutes after administration of the dantrolene, the ETCO2 had decreased to 34 mm Hg, heart rate was 85/min, and the temperature had dropped to 38.0°C (100.5°F). The masseter muscle rigidity and generalized muscular rigidity completely resolved. Fifty minutes after dantrolene administration, a repeated arterial blood gas analysis indicated that the respiratory acidosis had resolved; however, the potassium concentration was 6.1 mmol/L. The patient was again administered 10 U of regular insulin and 25 g of 50% dextrose. The blood pressure was 128/62 mm Hg, and the heart rate was 80/min.

Seventy minutes after treatment for suspected MH, the patient’s condition was stable, and he was transported by helicopter to a higher level of care. The surgeon and the anesthesia provider at the North Atlantic Treaty Organization (NATO) hospital at Kandahar Air Field, Afghanistan, were contacted by phone and informed of the intraoperative events. The patient was exubicated 9 hours after transport. On the following day, the patient returned to the operating room for definitive treatment of his fracture and closure of the wound. A nontriggering anesthetic was administered. His perioperative course was uneventful, and he was discharged 24 hours later to a local Afghan hospital. Further workup for MH was not available at the Afghan hospital.

Discussion

This report describes the first case of suspected MH in a trauma patient of Afghan nationality during Operation Enduring Freedom at a US forward combat surgical facility. This report also demonstrates the challenge of identifying and managing suspected MH in a trauma patient in an austere environment. Although there were signs suggestive of MH, there were many confounders that complicated the evaluation.

The clinical features of MH have been well documented. They result from hypermetabolism due to increased intracellular entry of calcium, after the patient is exposed to depolarizing muscle relaxants and/or volatile anesthetic agents. There is a wide variability in the time of symptom onset and overall clinical presentation of MH across the affected population. The reason for this is multifactorial. Carpenter and colleagues analyzed 23 RyR1 variants and found significant difference in MH phenotypes based on this genetic variation that may explain the variability in clinical presentation of MH after exposure to triggering agents. Furthermore, Hopkins suggested that modern anesthetic agents, especially sevo-flurane, tend to be associated with the delayed onset of MH (median, 60 minutes; range, 10-210 minutes) compared with halothane (median, 20 minutes; range, 5-45 minutes), and that nondepolarizing muscle relaxants

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may as well delay the onset and lower the maximum creatine kinase concentration. Support for the first finding also comes from Kunst et al,9 who investigated the effect of sevoflurane on calcium release from the sarcoplasmic reticulum, and reported that compared with halothane, sevoflurane induced smaller calcium release. Taken together, these findings may provide some explanations for the wide variability in the time of onset and the clinical features of reported MH cases.

The review by Larach et al1 has demonstrated unexplained hypercarbia to be the most frequent first or early sign of a suspected MH crisis, followed by sinus tachycardia and masseter muscle spasm. High or rapidly increasing temperature was present in 65% of the reported cases but was a first sign in less than 10% of the reports. In this case, the first presenting signs of possible MH event included hypercarbia, sinus tachycardia, and masseter muscle spasm. Although the patient’s temperature was mildly elevated, it did not appear to rapidly rise.

In an austere environment, the MH grading scale may assist clinicians in quantifying likelihood of the event. This numeric assessment tool, developed by Larach et al,9 assigns points as primary indicators of likelihood of the event, as follows: (1) rigidity (ie, generalized muscular rigidity = 15 points), (2) muscle breakdown (ie, elevated creatine kinase concentration > 20,000 IU in cases that included succinylcholine = 15 points; serum potassium level > 6 mEq/L = 3 points), (3) respiratory acidosis (ie, PaCO$_2$ > 60 mm Hg with appropriately controlled ventilation = 15 points), (4) temperature increases (ie, inappropriately rapid increase in temperature, in the anesthetist’s judgment = 15 points), (5) cardiac involvement (inappropriate sinus tachycardia = 3 points), (6) family history (ie, “positive” family history of MH in a first-degree relative = 15 points), and other indicators (ie, arterial pH < 7.25 = 10 points; base excess more than −8 mEq/L = 10 points; rapid reversal of MH signs with administration of dantrolene = 5 points). Scores of 35 to 49 are considered very likely, and scores of 50 or more are almost certain for the likelihood of an MH event.

Our patient was observed to have masseter and abdominal muscle rigidity (15 points), PaCO$_2$ greater than 60 mm Hg despite appropriately controlled ventilation (15 points), pH less than 7.25 (10 points), serum potassium level above 6 mEq/L (3 points), and rapid reversal of the suspected MH signs immediately after dantrolene (5 points). Using the scale, our case had a calculated raw score of 48, placing it in the “very likely” range for an MH event. The patient did receive 4 U of packed red blood cells, which may have contributed to the hyperkalemia,10 however, had we not included this finding in our score, the likelihood would have remained within the same range. Although spontaneous hypoventilation under general anesthesia combined with the large amounts of opioids administered could have initially contributed to the hypercarbia and respiratory acidosis, our patient’s PaCO$_2$ remained persistently above 60 mm Hg after he resumed controlled ventilation with high MV and high fresh gas flows. Administration of normal saline could have resulted in a hyperchloremic metabolic acidosis. The etiology of tachycardia in the acute trauma patient is multifactorial; hence we chose not to utilize it as the component of our MH grading scale. Furthermore, the creatine kinase and temperature elevations were not completely consistent with an MH presentation. Additionally, it is possible that the muscular rigidity could have been partially explained by emergence from anesthesia. However, the signs and symptoms suggesting MH did rapidly resolve after the administration of dantrolene. Thus, a score of 48 on the MH Clinical Grading Scale may be generous. Without confirmation with a caffeine halothane contraction test11 and/or genetic testing2 for RyR1 or CACNA1S, we cannot confirm that the patient truly experienced an MH event.

Military anesthesia providers in an austere combat environment face severe constraints of human and equipment resources. Typically, forward deployed surgical facilities in Afghanistan are staffed with only 2 anesthesia providers, 2 general trauma surgeons, 1 orthopedic surgeon, and 1 to 2 general medical practitioners. Diagnostic capabilities are also extremely limited. Other support personnel may also be tasked with multiple duties during the mass casualty events. Scenarios in which several patients must expeditiously undergo damage control procedures are not uncommon, thus severely limiting the time to conduct adequate preanesthetic risk assessment. Another problem we often encounter while rendering care for combat trauma victims is the language barrier between patient and provider, further limiting our ability to perform thorough preoperative anesthesia evaluation. Identification of MH-susceptible individuals and dedication of limited resources to MH events may be very difficult because of the unique circumstances of our practice. It is imperative then to maintain a very high index of suspicion for MH when dealing with hypermetabolic crises of unknown causes and also to be adequately prepared to implement quick and aggressive therapy for the earliest indications of suspected MH. Additionally, military anesthesia providers should ensure they have an adequate supply of dantrolene and consider incorporating simulated MH events into mass casualty drills.

**Conclusion**

Malignant hyperthermia triggered by modern anesthetic agents may have a delayed and insidious onset. Furthermore, as this case demonstrates, detection and differential diagnosis of a suspected MH event may be challenging in the acute trauma patient in an austere environment that has limited resources and capabilities.
Therefore, it is imperative under these circumstances that anesthesia providers have a high level of suspicion for an MH event and be prepared to rapidly treat suspected cases with dantrolene. Delay in the definitive treatment might result in a catastrophic outcome.

REFERENCES

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