Malignant Hyperthermia Like Manifestations during Management of Refractory Status Epilepticus

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Abstract

Management of refractory status epilepticus is challenging for a neurointensivist consequent to systemic complexities associated with various drugs and modalities involved in its treatment. We report one such case that manifested with multiple signs of malignant hyperthermia following use of isoflurane to control seizures. However, the delayed and random occurrence of the signs and negative genetic test report raises doubts regarding the final diagnosis. Delayed presentation of malignant hyperthermia has been reported earlier. Unavailability of dantrolene sodium handily is a major hurdle in treating such cases. We enumerate management of the patient in our intensive care unit.

Keywords
- status epilepticus
- malignant hyperthermia
- delayed malignant hyperthermia
- isoflurane

Introduction

Refractory status epilepticus (RSE) is characterized by prolonged episodes of seizures refractory to first- and second-line anticonvulsants. Its management involves intravenous (IV) anesthetic agents and other alternative approaches. Volatile anesthetic agents are increasingly used for RSE. We report a case of probable malignant hyperthermia (MH) with the use of isoflurane for the management of RSE.

Case Report

A 29-year-old female presented with recurrent complex partial seizures progressing to secondary generalization. She was started on fosphenytoin and levetiracetam. Magnetic resonance imaging of brain was normal. With no improvement in seizure control, she was admitted to intensive care unit (ICU) and anticonvulsants were escalated rapidly to phenobarbital, clobazam, sodium valproate, carbamazepine, lacosamide, and perampanel. Though convulsions ceased, bedside continuous electroencephalogram (cEEG) showed nonconvulsive status epilepticus. She was started on IV midazolam infusion (0.3mg/kg/h). However, cEEG showed persistent nonconvulsive epileptiform discharges. Midazolam was discontinued after 24 hours and IV thiopentone infusion initiated at 4mg/kg/h following bolus of 1 mg/kg. Though suppression of spike activity could be achieved on cEEG, it recurred on tapering the infusion and subsequently became refractory even at higher doses (5mg/kg/h). Consequently, thiopentone was stopped after 36 hours. Alternative approaches like IV ketamine, magnesium sulfate, and immunoglobulin therapy[1] were administered with no benefit.

On day 4 of admission, inhalational anesthesia with isoflurane was initiated at 1% concentration with fresh gas flows of 1 L/min using an anesthesia workstation. Heart rate (HR) was 105 beats per minute (BPM), blood pressure 112/68 mm Hg, and temperature 100.8°F (►**Fig. 1**) at initiation. Subsequently, the cEEG spikes disappeared. Four hours after

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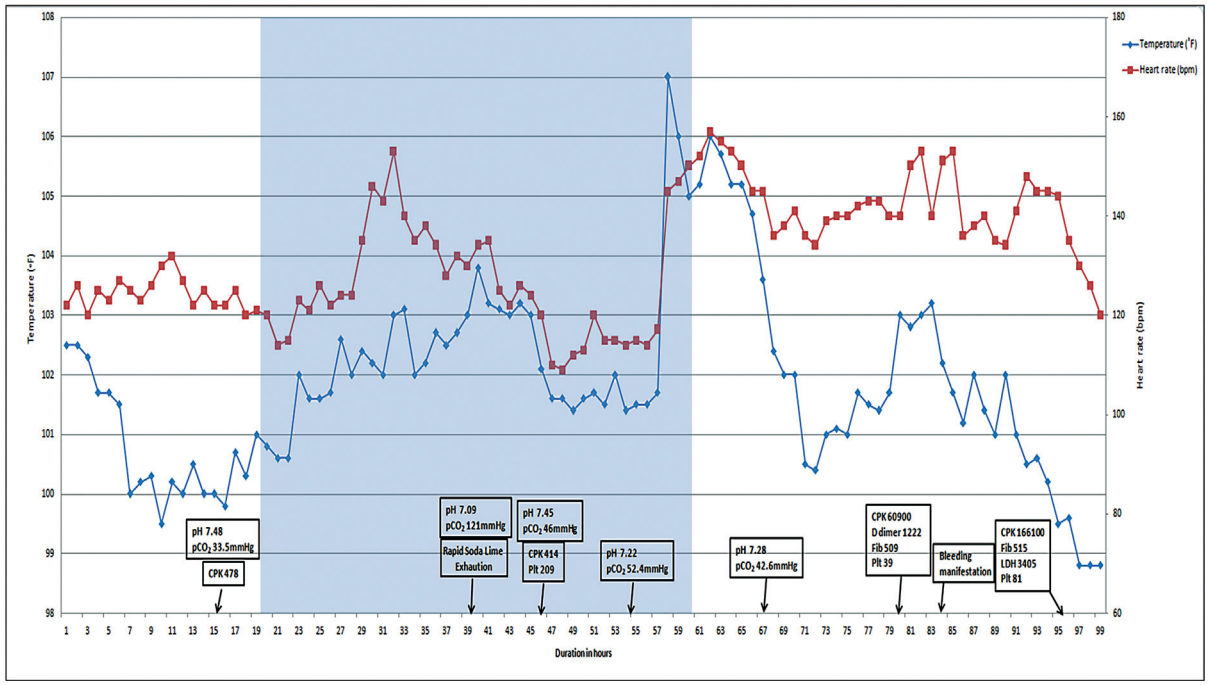

Fig. 1 Temperature and heart rate changes before, during, and after isoflurane anesthesia. The shaded area represents period of isoflurane administration. Arterial blood gas parameters and other laboratory parameters at different time points labeled. CPK, creatine phosphokinase (U/L); Fib, fibrinogen (mg/dL) and D-dimer (ng/mL); LDH, lactate dehydrogenase; pCO2, partial pressure of carbon dioxide; Plt, platelet count ($\times 10^9$/L).

commencing isoflurane, temperature recorded was 102°F and ranged between 102 and 103°F (►**Fig. 1**) thenceforth. She was managed with IV paracetamol and cold sponging.

Twenty hours after isoflurane initiation, soda lime exhaustion occurred alarmingly fast requiring replacement every 4 hours. Arterial blood gas (ABG) showed severe respiratory acidosis with pH 7.09, partial pressure of oxygen 109 mm Hg, and partial pressure of carbon dioxide (paCO2) 121 mm Hg. Ventilator parameters were adjusted to increase minute ventilation, which improved ABG parameters (►**Fig. 1**). Temperature ranged between 101 and 102°F. Chest X-ray was normal.

Thirty-eight hours after isoflurane initiation, temperature peaked to 107°F. Cold IV fluids administration, surface cooling, and cold saline gastric lavage were done. Sepsis workup was initiated. HR ranged between 140 and 160 BPM. A strong suspicion of MH was considered and isoflurane discontinued 39 hours after initiation. Dantrolene sodium is not available at our institute and could not be sourced expeditiously.

Temperature and hemodynamic parameters settled within normal range over next few hours (►**Fig. 1**). cEEG showed occasional spike discharges which the neurologist accepted as good control of seizures and continued on IV anticonvulsants. Twelve hours after isoflurane cessation, she developed bleeding manifestation. There was oozing from all puncture sites, hematuria, and blood-tinged oral secretions. Creatine phosphokinase (CPK) increased exponentially reaching a peak of 166,100U/L 36 hours after isoflurane was stopped. Lactate dehydrogenase, D-dimer, and fibrinogen were elevated and platelet counts declined (►**Fig. 1**). Packed red blood cells, fresh frozen plasma, and single donor platelets were transfused and the oozing subsided in 8 hours. Coombs test was negative. Urine output and renal function tests were normal and lactates on ABG remained less than 1 mmol/L throughout the ICU stay. Cultures of blood, urine, and tracheal aspirates done periodically did not show any growth.

The seizure duration reduced progressively and ceased in 3 weeks. She was weaned from ventilator and discharged with tracheostomy tube in situ. At 6 months follow-up, she had score of 3 on modified Rankin scale.

DNA testing (targeted gene sequencing) was done to evaluate for pathogenic gene variations of MH. It was negative for any specific gene abnormality.

Discussion

MH is an inherited disorder of the skeletal muscle where abnormal calcium homeostasis occurs in response to triggers such as succinylcholine and volatile inhalation anesthetic agents. It can have a highly variable clinical presentation and delayed onset[2–4] making definitive diagnosis challenging.

Based on a grading scale developed by Larach et al[5] incorporating 15 clinical and 10 laboratory parameters to predict MH susceptibility, our patient's total score was 58. Parameters included were elevated CPK more than 10,000 IU, arterial paCO2 more than 60 mm Hg, inappropriately rapid increase in temperature, inappropriate sinus tachycardia, and arterial pH less than 7.25. This indicates an "almost certain" likelihood of MH corresponding to MH rank 6.

Elevated HR (110–120 BPM) and temperature spikes (100–103°F) were present prior to commencing isoflurane (►**Fig. 1**). This could be attributed to continuous seizure

activity or infection owing to presence of multiple sources (endotracheal tube, central venous catheter, invasive arterial pressure line, and Foley catheter). The bleeding manifestation occurred 30 hours after peak temperature (107°F) and 12 hours after normal temperature was recorded. Myoglobinuria, rhabdomyolysis, and coagulopathy can also occur in patients with status epilepticus that were confounding factors to diagnosis. The lack of more substantial metabolic acidosis is puzzling considering the degree of rhabdomyolysis since bioenergetic failure at the cellular level is expected.

Delayed presentation of MH has been reported previously with isoflurane where the duration of onset was around 5 hours.[2–4] All patients survived following administration of dantrolene sodium, the drug of choice for MH. However, there are reports of complete recovery in few cases without use of dantrolene.[6,7]

Atypical presentation of MH has been reported where presentation was myoglobinuria and delayed hyperpyrexia without typical signs of tachycardia, tachypnea, and increased end-tidal carbon dioxide.[8]

In a recent report, five cases of MH reported in the Indian subcontinent so far have all survived despite dantrolene being administered in only one patient.[9]

Genetic testing of MH is fraught with complexities due to involvement of multiple genes, multiple variations within the genes, and more than one gene contributing to the susceptibility.[10] The sensitivity for diagnosing MH on DNA screening is as low as 50%. Thus, a negative report cannot conclusively rule out MH susceptibility. The gold standard for diagnosing MH, caffeine halothane contracture testing, was not done in this patient as consent for muscle biopsy was denied.

Conclusion

Clinical manifestations in our case point toward delayed MH, which remained unconfirmed by genetic laboratory tests. The emphasis must be on timely diagnosis and supportive measures to strive for a favorable outcome. Though use of volatile anesthetics for attenuation of seizure activity was effective in our patient, it is imperative to exercise caution when employing this therapy.

Conflict of Interest
None declared.

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