A Fulminant Malignant Hyperthermia Episode in a Patient with Ryanodine Receptor Gene Mutation p.Tyr522Ser

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Malignant hyperthermia (MH) has been a known anesthetic risk since 1960.1 As the knowledge of MH pathophysiology has increased, specific therapeutic action has become available. MH might be viewed by some as a disease of historic interest only, as the use of triggering drugs (i.e., volatile anesthetics and succinylcholine) has decreased. This case report emphasizes the importance of MH in anesthetic practice today and suggests new diagnostic options to establish MH susceptibility (MHS).

CASE DESCRIPTION

A 37-yr-old male patient presented with a traumatic lesion of the left bursa olecrani and was scheduled for elective bursectomy. The only concomitant disease was exertional asthma. The patient weighed 75 kg and his Body Mass Index was 26 kg/m².

The patient was transferred to the operating room after receiving 7.5 mg midazolam orally 1 h before induction. Standard monitoring, including noninvasive arterial blood pressure, five-lead electrocardiogram, and measurement of arterial oxygen saturation, was placed, as well as peripheral venous access. Anesthesia was induced with 2 mg/kg propofol and 0.25 mg fentanyl. A classical laryngeal mask was inserted. Anesthesia was maintained with sevoflurane (maximal end-tidal concentration of 2.5%) in an oxygen/air mixture of 1 L/min each. The patient received 75 mg of IV diclofenac. The patient’s lungs were ventilated in a pressure-controlled mode (maximal inspiratory pressure 13 mm Hg), maintaining a respiratory volume of 4.9 L/min and an end-tidal CO₂ concentration of 5.5 kPa. Surgery started 25 min after induction under stable patient conditions.

Thirty minutes after the start of surgery, end-tidal CO₂ began to increase rapidly, reaching a maximum of 24 kPa after 5 min despite an increase in minute ventilation to 18 L/min. His temperature rapidly increased from 36.5°C to 40°C. The patient showed no sign of muscular rigidity. MH was suspected after the initial increase of CO₂. Sevoflurane was immediately discontinued and the patient’s lungs were ventilated with 100% O₂. Surgery was quickly completed. Dantrolene was prepared and administered (4 × 2.5 mg/kg; total = 800 mg). An arterial line was inserted into the left radial artery and blood was withdrawn for blood gas analysis (Table 1). The patient’s trachea was intubated after the administration of propofol (2 mg/kg) and rocuronium (0.9 mg/kg). Anesthesia was maintained with propofol. A volume-controlled mechanical ventilation mode with a tidal volume of 800 mL and an increasing respiratory rate were used in order to reduce end-tidal CO₂. Hyperkalemia of 6.6 mmol/L at a pH of 7.26 was treated with 100 mL of 8.4% sodium bicarbonate. A urethral catheter and a nasogastric tube were placed, and cooling of the patient was initiated using cold infusions of 0.9 NaCl ice water given via a nasogastric tube and applied to the skin surface. With these measures, his temperature decreased to 37.5°C, metabolic acidosis was rapidly reversed, and end-tidal CO₂ decreased to 4.9 kPa. One hour after the first CO₂ increase, the patient was transferred to the intensive care unit in stable cardiopulmonary condition without inotropic support.

As a result of rhabdomyolysis maximal creatine kinase 1700 IU/L, normal range below 195; myoglobin 24 nmol/L, normal range below 3.9 and an increase in blood urea nitrogen (9.7 mmol/L) and creatinine (123 μmol/L), venous hemodiafiltration was initiated 3 h postoperatively and maintained for 16 h. The dantrolene infusion was continued with 10 mg/kg for 24 h and was discontinued 24 h after the event. Subsequently, his body temperature increased again to a maximum of 38.5°C without signs of...
The following exons were analyzed by automated sequencing: 8, 9, 14, 15, 19, 45, 46, 50, 53, 80, 100, 101, 102, and 103. Mutations p.C35R, p.A163C, p.I403M, p.D2730G were investigated by restriction fragment length polymorphism analysis. The patient was found to be a heterozygous carrier of mutation p.Tyr522Ser in exon 14. This result was confirmed in a second reaction. There were no other mutations or polymorphisms detected.

The patient was given a warning card. He was educated about the dominant inheritance of MH and the possibility of molecular genetic testing within his family.

**DISCUSSION**

Although MH has been well described in the literature, it is still important to report clinical MH episodes so that anesthesiologists do not believe MH to be a “solved problem.” For example, there was no refresher course on MH at the 2007 annual meeting of the American Society of Anesthesiologists. MH still exists and remains a real threat to our patients, even healthy young patients undergoing general anesthesia for minor procedures. Complete monitoring must always include end-tidal CO₂ and temperature, if the disease is to be rapidly recognized.

According to the guidelines of the EMHG, MHS must be tested by an open muscle biopsy followed by the in vitro contracture test. Molecular genetic testing for MHS is recommended in families known to carry MH causative mutations. The in vitro contracture test is performed on muscle biopsies thus involving many different muscular proteins, whereas molecular genetic testing focuses on one or two single genes. The molecular genetic basis of MH can be identified in approximately 50% of MH families. Only few MH-associated mutations have been proven causative. Therefore, molecular genetic investigations have a high probability to be nonconclusive in patients with suspected clinical MH episodes. Absence of RYR1 mutations does not exclude MHS and, thus, contracture testing has to follow negative molecular genetic investigations. This is not always understood by the patient and/or the referring physician, which may place the patient at risk for falsely believing that the patient is not MHS. Obviously, the chance to identify an MH causative mutation increases with the probability of a true MH event. A MH episode can be classified according to the clinical grading scale, which revealed 76 points in our patient, classifying his episode as “almost certain” MH. Due to the clinical picture and because the patient refused a muscle biopsy, we could not follow the EMHG guidelines and had to proceed directly to molecular genetic analysis.

The identified mutation, p.Tyr522Ser, is a rare MH-associated mutation. It was first described in a French family, and was confirmed to be MH causative by Tong et al. Mutation p.Tyr522Ser was used in the first murine model of MH by Chelu et al. In mice heterozygous for p.Tyr522Ser, fatal MH can be triggered by volatile anesthetics and by heat stress. This case report confirms the causative nature of this mutation in humans.

In conclusion, MH is not a “historic disease” and remains a risk of general anesthesia if triggering drugs are used. Awareness of MH and rapid recognition of clinical signs, together with symptomatic and specific therapy, is lifesaving. Alerting the patient to the likelihood of being MHS is insufficient. Laboratory testing to establish an MH diagnosis is important, especially in a condition with autosomal dominant inheritance. A negative MH diagnosis relieves the burden of MHS for the patient himself and his family. In cases with symptoms very indicative of true MH, an a priori molecular genetic investigation may be an appropriate alternative to muscle biopsy and contracture testing. However, contracture testing must be used if the molecular genetic investigation is negative.

**REFERENCES**


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**Table 1. Results of Arterial Blood Gas Analysis**

<table>
<thead>
<tr>
<th>Time after induction of anesthesia (h)</th>
<th>pH</th>
<th>pCO₂ (kPa)</th>
<th>pO₂ (kPa)</th>
<th>pCO₂ (kPa)</th>
<th>pH</th>
<th>Lactate (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>6.98</td>
<td>16.2</td>
<td>40.5</td>
<td>18.9</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>1.5 h</td>
<td>7.26</td>
<td>6.1</td>
<td>60.4</td>
<td>19.0</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>7.43</td>
<td>4.12</td>
<td>77.6</td>
<td>21.8</td>
<td>2.35</td>
<td></td>
</tr>
<tr>
<td>7 h</td>
<td>7.47</td>
<td>4.53</td>
<td>19.9</td>
<td>25.4</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>17 h</td>
<td>7.42</td>
<td>5.78</td>
<td>19.5</td>
<td>27.0</td>
<td>0.82</td>
<td></td>
</tr>
</tbody>
</table>

Time in hours after induction of anesthesia, signs of malignant hyperthermia (MH) started 1 h after induction.

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Metabolic acidosis, requiring administration of an additional 10 mg/kg 24 h dantrolene for another 24 h. The patient developed a cubital phlebitis on his left arm after accidental infiltration of the dantrolene infusion. His C-reactive protein increased from a preoperative value of 10.2 mg/L to 192 mg/L for 48 h postoperatively. The patient was sedated with propofol 100–300 mg/h during the first 36 h of his intensive care unit stay. The trachea was extubated on the second postoperative day, 50 h after the MH event. Creatine kinase and myoglobin returned to normal levels on postoperative day 5 and 3, respectively. The following day the patient was transferred to the regular surgical ward and was discharged 8 days later in good physical condition.

With the patient’s consent, an EDTA blood sample was drawn for molecular genetic analysis. The skeletal muscle type ryanodine receptor (RYR1) is the primary locus of MH. Mutation detection was performed in the Swiss MH investigation center by amplification of genomic DNA using the polymerase chain reaction according to previously described conditions for polymerase chain reaction and oligonucleotides. RYR1 was investigated for MH causative mutations, as defined by the European MH Group (EMHG). The following exons were analyzed by automated sequencing: 8, 9, 14, 15, 19, 45, 46, 50, 53, 80, 100, 101, 102, and 103. Mutations p.C35R, p.A163C, p.I403M, p.D2730G were investigated by restriction fragment length polymorphism analysis. The patient was found to be a heterozygous carrier of mutation p.Tyr522Ser in exon 14. This result was confirmed in a second reaction. There were no other mutations or polymorphisms detected.

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