

Clinical treatment of malignant hyperthermia in three cases

TAO PAN, WENLI JI, MENGQI NIE and YANG LI

Department of Intensive Care Medicine, Xiangyang Hospital Affiliated to
Hubei University of Medicine, Wuhan, Hubei 441000, P.R. China

Received February 8, 2016; Accepted September 1, 2016

DOI: 10.3892/etm.2016.3712

Abstract. Malignant hyperthermia (MH) is a rare life threatening inherited disorder that is triggered by drugs used for general anesthesia in susceptible persons. The symptoms include rapid increase of body temperature and severe muscle contractions. The present study includes 3 cases of MH and highlights the timely identification of symptoms for rescuing the patient. In case I, a 7-year-old male child underwent surgery with ketamine at a dose of 250 mg. After 4 h of operation, the child went through convulsions, high fever and succumbed within a few hours. High fever was not detected in a timely manner, which is one of the main symptoms of MH. In case II, a 12-year-old male child had convulsions and high fever after simple surgery caused by MH. Once confirmed, immediate measures were taken to lower the body temperature and the child was rescued. In case III, a male 57-year-old was admitted to hospital due to paraplegia. The patient underwent more critical conditions once symptoms of MH appeared. Additionally, antidote dantrolene was unavailable in the first and third case; thus, the progression of disease was not alleviated although active symptomatic and supportive treatment were employed.

Case reports

Case report I. The patient was a male aged 7 years and had a body weight of 28 kg. He was admitted to hospital on July 9, 2000 due to right side inguinal hernia. Preoperative blood routine examination was normal and he was given high ligation of hernial sac three days after admission. Only 0.5 h before surgery, 30 mg luminal and 0.2 mg atropine was injected intramuscularly, and 50 mg ketamine and 3 mg midazolam for anesthesia was injected intravenously. However, due to poor anesthetic effect, ketamine was added twice, each time

100 mg. The surgery lasted 30 min and the child in surgery displayed stable vital signs, with a total capacity of ketamine 250 mg. The child was unconscious after the operation. At 1:40 p.m., convulsions and high fever occurred, and his body temperature reached 40.2°C. Physical cooling and antipyretic drugs showed poor results. At 5:00 p.m., he was transferred into the ICU. After admission to the ICU, the child suffered persistent high fever and his heart rate was 140-160 times/min, breathing 40-45 times/min, blood pressure 82/40 mmHg (1 mmHg=0.133 kPa), oxygen saturation fluctuated between 80-84%, lips and ends of limbs showed cyanosis, skin temperature was low, the skin circulation was poor, isocoria and round pupils were 2.5 mm and was unresponsive to light, lung sputum was audible and there was abundant bloody sputum in the airway. A full investigation of DIC showed that PT extended more than 3 min, fibrinogen 1.5 g/l, blood routine examination demonstrated leukocytes 13.9 g/l, platelets $3.2 \times 10^9 \text{ l}^{-1}$, blood gas check showed carbon dioxide partial pressure of 55 mmHg, creatine kinase 17,000 U/l, after treatment such as respiratory, circulatory support, mannitol dehydration, heparin anticoagulation, 654-2 microcirculation improvement, the result proved to be ineffective. The child with disorders of consciousness gradually deepened, and his heart rate reached 180 times/min, blood pressure 40/30 mmHg. At 4:00 a.m. of July 13, the child's heart rate, blood pressure decreased significantly (heart rate 38 times/min, blood pressure 20/10 mmHg), epinephrine was immediately injected intravenously and intermittently, along with sustained chest compressions, but the result was ineffective and the child was declared clinically dead at 4:35 a.m.

Case report II. The patient was a male aged 12 years. He was admitted to hospital on July 8, 2010 due to right side inguinal hernia. On the day he was hospitalized he received high ligation of hernial sac under continuous epidural anesthesia sac ligation. Half an hour before surgery, 50 mg luminal and 0.5 mg atropine was injected intramuscularly, after successful puncture and catheterization between L2-L3 intervertebral space, the child was given 5 ml 0.894% ropivacaine and 2% lidocaine mixture, no abnormality was observed within 5 min, the aforementioned drugs were given in fractions with a total of 10 ml. The surgery lasted for 1.5 h and anesthesia lasted for 3 h. After the operation, the child suffered convulsions, high fever, and his body temperature reached 40.7°C. After being transferred to ICU, the child suffered persistent

Correspondence to: Dr Wenli Ji, Department of Intensive Care Medicine, Xiangyang Hospital Affiliated to Hubei University of Medicine, 15 Jiefang Road, Wuhan, Hubei 441000, P.R. China
E-mail: 1366346747@qq.com

Key words: malignant hyperthermia, clinical case, anesthesia, fever, ketamine

high fever, his heart rate stayed at 170 times/min, breathing was 51 times/min, blood pressure 90/57 mmHg, oxygen saturation fluctuated at around 50%. He was unconscious and isocoria and round pupils was 2.5 mm, and was unresponsive to light. His lips showed cyanosis, his ends of limbs were cold, breathing sound of lungs was clear and no wet or dry rales were heard. The heart was pounding fast, rhythm was tidy, abdomen was soft, liver and spleen were not touched and muscle tension of limbs was normal, bilateral Pap showed negative sign. Blood gas showed pH 7.289, carbon dioxide partial pressure 65 mmHg, BE-12.5/l, a full DIC showed PT18.8 S, APTT47.9S, DD 1,128 $\mu\text{g/l}$, blood routine examination, and electrolytes were normal. Creatine kinase check was 1,941.20 U/l. After admission to ICU, it was supposed that the child's high fever was caused by lidocaine-induced malignant hyperthermia (MH), thus immediate measures were taken to lower his temperature. Additionally, positive efforts were made to administer dantrolene, and gave treatments such as respiratory, circulatory support, blood circulation (lower right), microcirculation (phenol phentolamine) improvement, anticoagulation (LMWH), anti-infection, dehydration, renal protection, and CRRT treatment. On July 9, creatine kinase check was 70391.2013/l, LDH 2226.90 U/l, on July 11, creatine kinase check was 14,080 U/l, LDH 551 U/l. On July 12, the creatine kinase check was 3919.60 U/l, the next day it was 1,865.40 U/l, the day thereafter 331.20 U/l and on July 18 it dropped to 191.90 U/l. In addition, on July 18, head CT examination was normal. Eventually on July 20, the child was transferred from ICU with a conscious mind and residual mild neuropsychiatric symptoms. On July 22, as the head MRI showed increased T2 signal. Finally, on August 13, the child was discharged.

Case report III. The patient was a male aged 57 years. He was admitted to the hospital at 12:00 p.m. of June 17, 2011 due to paraplegia of both lower extremities caused by abdominal trauma for over 4 h. His physical examination at the admission showed a body temperature of 37°C, P 88 times/min, R 22 times/min, BP 105/80 mmHg. The patient was conscious and his neck was soft, chest squeeze sign 1, sound of breathing in both lungs was clear, no wet and dry rales were heard. The heart sound was strong and no noise was heard, abdomen was soft, no tenderness, no rebound tenderness, shifting dullness was negative. Myodynamia of upper limbs was grade 4, muscle strength of lower limbs was zero grade, muscle tone was normal, below the inguinal surface, feeling disappeared, knee tendon and tendon reflexes disappeared and pathological reflex was not elicited. The patient's limbs were not injured. Supplementary examinations were also performed, which clarified that lumbar spine had no fracture, while the lumbar vertebra MRI showed a mild protrusion of lumbar 5 sacrum I of the intervertebral disc. After 0.5 h of admission, the patient revealed abdominal pain and discomfort, abdominal puncture showed non-condensable blood, emergent B-ultrasound showed large amount of fluid in abdominal cavity. Urgent laparotomy was conducted under general anesthesia intubation, extensive contusions were observed in the stomach, duodenum, transverse colon and pancreas and lacerations in transverse mesocolon, gastroepiploic, retroperitoneal hematoma, intra-abdominal

hemorrhage and blood clots totaled about 2,000 ml. Repair surgery on gastroepiploic and transverse mesocolon was conducted and the patient was transferred into ICU after the surgery. In the operation, propofol and vecuronium were injected intravenously for anesthesia instead of using inhaled anesthetics (such as enflurane and isoflurane) ketamine, and lidocaine. After being hospitalized for 4 h, the patient's temperature rose to 38.6°C, which increased further after 9 h to 39.6°C. After being admitted to ICU, blood gas showed pH 7.01, carbon dioxide partial pressure was 73 mmHg (with ventilator assisted breathing), oxygen partial pressure 183 mmHg, blood sodium 134 mmol/l, serum potassium 7.3 mmol/l, ionized calcium 1.02 mmol/l, glucose 12.3 mmol/l, lactic acid 7.9 mmol/l, bicarbonate 18.4 mmol/l, BE-13.2 mmol/l, hemoglobin 109 g/l. Creatine kinase level was 14 888.7 U/l, lactate dehydrogenase 834.2 U/l, aspartate aminotransferase 314.5 U/l, the color of urine was normal. At 8:30 p.m. of June 17, the patient recovered consciousness, myodynamia of his upper limbs increased to five grade, his lower limbs had no activity, and his muscle was stiff with high muscular tension, pathological reflex was negative. ECG showed high edge of T wave, the intravenous injection of high glucose, sugar calcium and continuous intravenous infusion of sodium bicarbonate produced poor results. Serum potassium fluctuated between 6.2-7.6 mmol/l. At 9:30 p.m., electrocardiographic monitoring showed that the patient's heart rate gradually slowed down to 60-80 times/min, the intravenous injection of high glucose, sugar calcium and continuous intravenous infusion of sodium bicarbonate still produced poor result. At 9:45 a.m. of June 18, the patient suffered ventricular fibrillation, immediate cardiac compressions, defibrillation and intermittent intravenous injection of epinephrine were given to him. After 20 min, the patient transformed from ventricular fibrillation to sinus rhythm. Review of chest with B-ultrasound showed no pleural effusion and pericardial effusion, but a little peritoneal effusion and subcapsular fluid under the left kidney. At 10:00 p.m., color of urine was dark brown and the quantity of urine was scanty, myoglobin rose to 1,200 ng/ml. After conducting blood purification therapy, patient's serum potassium gradually returned to normal but the patient soon appeared MOF and his blood pressure could not be maintained at normal level under high dose of dopamine. The patient appeared polypnea and heart rate was 36 times/min, his blood oxygen was 75% at higher oxygen concentrations, clotting mechanism was abnormal (platelets reduced from $138 \times 10^9 \text{ l}^{-1}$ to $78 \times 10^9 \text{ l}^{-1}$, APTT61.3s, DD 1 096 $\mu\text{g/l}$). On June 19, due to critical condition, the patient's family signed away the rescue and the patient was automatically discharged.

Discussion

MH is a rare complication of anesthesia, with an incidence frequency of 1:10,000 (1-3). However, the incidence of patients with genetic abnormalities can reach 1/3,000 (4,5). MH progresses rapidly once it occurs and causes death due to multiple organ failure (MOF) (6). In the 1960's, the mortality of MH reached up to 90%. Improving understanding and treatment of MH is the incumbent responsibility of doctors who deal with critically ill patients (7-9). MH demonstrates

high metabolic syndrome of skeletal muscle induced by inhaling potent general anesthetics and depolarizing muscle relaxant succinylcholine, including quick high fever, rigid skeletal muscle, tachypnea, tachycardia, rhabdomyolysis, acid poisoning and hyperkalemia (10-12). The most common drugs that easily induce MH are halothane and succinylcholine, in addition, methoxyflurane, enflurane, isoflurane, desflurane, sevoflurane, ether, cyclopropane, trichlorethylene, gallamine triethiodide, D-tubocurarine, lidocaine and ropivacaine can also cause MH (13). It is also reported that MH may be induced by ketamine at home (14). Some congenital diseases such as idiopathic scoliosis, strabismus, ptosis, umbilical hernia, inguinal hernia and other diseases are prone to appear MH in anesthesia (15). At present, the gold standard for the diagnosis of MH is caffeine halothane skeletal muscle contraction experiment, which can only be conducted at Concord Hospital (16). When the caffeine halothane skeletal muscle contraction experiment is not practicable, we can assess clinical indicators of the MH to help us understand the possibility of MH. If the score is more than 50 points, the diagnosis is almost certain (17-19). For treatment of MH, the only approach is to immediately stop using inhaled anesthetic agent, make great efforts to lower the temperature, employ cooling drug with special effects dantrolene, to correct acidosis and electrolyte imbalance, stabilize hemodynamic, protect the function of kidneys and other organs (20).

In case 1, the child underwent a very simple surgery after dosage of ketamine was 250 mg. After the surgery, the child was not conscious. After 4 h of operation, the child suffered convulsions and high fever, 5 mg dexamethasone treatment turned out to be ineffective and rapid appearance of MOF led to the child's death. The child's convulsions and high fever were supposed to be caused by MH. The child had a history of excessive use of ketamine, no symptoms of infection and no infusion reactions. MH score for him reached 53 points and diagnosis of it was almost certain. In case 2, the patient's convulsions and high fever were also supposed to be caused by MH. The patient also had a history of the use of lidocaine with no symptoms of infection and no infusion reactions. His MH score was 53 points and diagnosis of MH was almost certain. In case 3, the patient was admitted to hospital due to paraplegia, when entering into ICU, his muscular tension of both lower limbs was high and his muscle was stiff and rigid, which could not be explained by spinal cord injury. The patient had no history of head trauma and no signs of head trauma and he was conscious. Traumatic brain also failed to explain that his muscular tension of both lower limbs was high and his muscle was stiff and rigid, the focus area of the patient's trauma was in the abdomen and not at the lower limbs, rhabdomyolysis could not be explained by muscle trauma although the patient had no family history of MH. Inhalation anesthetic, ketamine, lidocaine were not used in the operation, postoperative body temperature rose slowly, the total score of MH of the patient reached up to 65 points and the diagnosis for MH was almost certain. All these patient's clinical manifestations could only be explained by MH.

In the treatment of the first case of MH, unfortunately due to insufficient knowledge of the disease, high fever had not been detected timely (21). The symptomatic treatment of high fever was not enough, resulting in the child's death induced

by quick MOF. In the second case, due to more awareness of the disease, more attention was paid to monitor the patient's body temperature, so the patient's temperature abnormality was detected immediately, and he was transferred to the ICU as fast as possible. All measures were taken to cool his temperature (22,23) (physical cooling, drug defervesce, nasal feeding of brine ice, enema of brine ice, intravenous fluid at 4°C, sub-hypothermia hibernation, CRRT body temperature control) thus creating opportunities and conditions for successful treatment of the patient. In the treatment of the first and third case, special effect antidote dantrolene was unavailable, so the course of the disease could not be blocked although active symptomatic and supportive treatment was adopted, the patients still died. In case 2, after the onset of the disease, antidote dantrolene was contacted at once. The child's condition was significantly alleviated after oral administration of dantrolene. Active cooling and application of special effect antidote dantrolene played a key role in the successful treatment of the child. The survival of this patient was also related to large doses of CRRT + UTI (24-26). On one hand, CRRT treatment quickly and effectively controlled the patient's body temperature, whereas on the other hand, inflammatory mediators and myoglobin were quickly cleared by convection mechanism and thus the renal function was protected (27). The use of large dose of UTI stabilized the cell membrane and protected organ function (28). The combination of the two improved the success rate of case 2. The initial clinical manifestations of case 3 were not typical, DIC progressed rapidly, and the disease developed to MOF stage shortly, thus losing the opportunity for treatment.

References

1. Kamińska E, Janas A and Osica P: Malignant hyperthermia - problem in dental surgery. An introductory report. *Dev Period Med* 18: 483-488, 2014 (In Polish).
2. Riaz S, Kraeva N, Muldoon SM, Dowling J, Ho C, Petre MA, Parness J, Dirksen RT and Rosenberg H: Malignant hyperthermia and the clinical significance of type-I ryanodine receptor gene (RYR1) variants: proceedings of the 2013 MHAUS Scientific Conference. *Can J Anaesth* 61: 1040-1049, 2014.
3. Roesl C, Sato K, Schiemann A, Pollock N and Stowell KM: Functional characterisation of the R2452W ryanodine receptor variant associated with malignant hyperthermia susceptibility. *Cell Calcium* 56: 195-201, 2014.
4. Han H, Shao J and Zhang M: Diagnosis and treatment of malignant hyperthermia. *Chinese General Medical Council* 11: 314-317, 2008 (In Chinese).
5. Itoh K, Nishibe S, Usuda Y and Kitamura A: Suspected case of postoperative malignant hyperthermia treated with dantrolene one week after neurosurgery. *Masui* 63: 1153-1155, 2014 (In Japanese).
6. Wang Y, Guo X and Luo A: Diagnosis and treatment progress of malignant hyperthermia. *Chinese J Anesthesiol* 26: 92-94, 2006 (In Chinese).
7. Aderibigbe T, Lang BH, Rosenberg H, Chen Q and Li G: Cost-effectiveness analysis of stocking dantrolene in ambulatory surgery centers for the treatment of malignant hyperthermia. *Anesthesiology* 120: 1333-1338, 2014.
8. Brislin RP and Theroux MC: Core myopathies and malignant hyperthermia susceptibility: a review. *Paediatr Anaesth* 23: 834-841, 2013.
9. Nelson P and Litman RS: Malignant hyperthermia in children: an analysis of the North American malignant hyperthermia registry. *Anesth Analg* 118: 369-374, 2014.
10. Hoppe K, Schleip R, Lehmann-Horn F, Jäger H and Klingler W: Contractile elements in muscular fascial tissue - implications for in-vitro contracture testing for malignant hyperthermia. *Anaesthesia* 69: 1002-1008, 2014.

11. Kazantseva AA and Lebedinskiĭ KM: Modern diagnostic approaches to malignant hyperthermia susceptibility. *Anesteziol Reanimatol* 59: 64-68, 2014 (In Russian).
12. Gillies RL, Bjorksten AR, Du Sart D and Hockey BM: Analysis of the entire ryanodine receptor type 1 and alpha 1 subunit of the dihydropyridine receptor (CACNA1S) coding regions for variants associated with malignant hyperthermia in Australian families. *Anaesth Intensive Care* 43: 157-166, 2015.
13. Yang Z, Wu X and Huang Z: Retrospective comparative analysis of malignant hyperthermia. *Clin Med (Northfield, IL)* 30: 8-11, 2010.
14. Wang YL, Guo XY and Luo AL: Malignant hyperthermia in Mainland China: an analysis of 34 cases. *Chinese Anesthesiol* 26: 107-109, 2006 (In Chinese).
15. Larach MG, Brandom BW, Allen GC, Gronert GA and Lehman EB: Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesthesiology* 108: 603-611, 2008.
16. Nakamura N, Ueda T, Ishikawa R, Tasaka Y, Fukuuchi K and Sato N: Malignant hyperthermia developing during esophageal resection in an 82-year-old man. *J Anesth* 22: 464-466, 2008.
17. Riazi S, Larach MG, Hu C, Wijesundera D, Massey C and Kraeva N: Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. *Anesth Analg* 118: 381-387, 2014.
18. Vigilante JA: Case report: clearance to dive for a naval candidate with family history of malignant hyperthermia. *Undersea Hyperb Med* 40: 365-369, 2013.
19. Sousa CS and Cunha AL: Knowledge of nursing professionals of a surgical center regarding malignant hyperthermia. *Rev Gaucha Enferm* 35: 43-48, 2014 (In Portuguese).
20. Rosero EB, Adesanya AO, Timaran CH and Joshi GP: Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. *Anesthesiology* 110: 89-94, 2009.
21. Bina S, Capacchione J, Munkhuu B, Muldoon S and Bünger R: Is lymphocyte adenosine a diagnostic marker of clinical malignant hyperthermia? A pilot study. *Crit Care Med* 43: 584-593, 2015.
22. Larach MG, Brandom BW, Allen GC, Gronert GA and Lehman EB: Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007-2012: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesth Analg* 119: 1359-1366, 2014.
23. Liu Z, Fang L and Teng Y: Clinical diagnosis and treatment of malignant Hyperthermia. *J Emerg Med* 16: 1226-1227, 2010.
24. Altamirano F, Eltit JM, Robin G, Linares N, Ding X, Pessah IN, Allen PD and López JR: Ca^{2+} influx via the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger is enhanced in malignant hyperthermia skeletal muscle. *J Biol Chem* 289: 19180-19190, 2014.
25. Cain CL, Riess ML, Gettrust L and Novalija J: Malignant hyperthermia crisis: optimizing patient outcomes through simulation and interdisciplinary collaboration. *AORN J*: 99: 301-308, 2014.
26. Shaaban S, Ramos-Platt L, Gilles FH, Chan WM, Andrews C, De Girolami U, Demer J and Engle EC: RYR1 mutations as a cause of ophthalmoplegia, facial weakness, and malignant hyperthermia. *JAMA Ophthalmol* 131: 1532-1540, 2013.
27. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van SH, Ronco C and Kellum JA: Continuous renal replacement therapy: A worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. Kidney) investigators. *Intensive Care Med* 33: 1563-1570, 2007.
28. Sheng R, Jiao JJ and Ting W: Research on multiple organ dysfunction syndrome with Ulinastatin and continuous blood purification therapy. *J Emerg Med* 17: 622-626, 2008.