

Original article

Clinical features and diagnosis for Chinese cases with malignant hyperthermia: a case cluster from 2005 to 2007

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Keywords: malignant hyperthermia; intraoperative complications; diagnosis

Background Malignant hyperthermia (MH), manifesting as MH crisis during and/or after general anesthesia, is a potentially fatal disorder in response to volatile anesthetics and depolarizing muscle relaxants. Though typical features of MH episode can provide clues for clinical diagnosis, MH susceptibility is confirmed by *in vitro* caffeine-halothane contracture test (CHCT) in western countries. It is traditionally thought that MH has less incidence and fewer typical characteristics in Chinese population than their western counterparts because of the different genetic background. In this study, we investigated the clinical features of MH in Chinese cases and applied the clinical grading scale and CHCT for diagnosis of MH.

Methods A cluster of three patients with MH, from January 2005 to December 2007, were included in the study. Common clinical presentations and the results of some lab examinations were reported in detail. The method of the clinical grading scale of diagnosis of MH was applied to estimate the qualitative likelihood of MH and predict MH susceptibility. Muscle fibers of femoral quadriceps of the patients were collected and CHCT was performed to confirm the diagnosis of MH.

Results The clinical grading scales of diagnosis of the disease for these cases were all ranked grade D6, suggesting almost diagnosed ones. And the results of caffeine test were positive correspondingly, indicating that the patients should be diagnosed as MH susceptibility (MHS) according to diagnostic criteria of the North America MH group, which were already confirmed by clinical presentations and biochemical results.

Conclusions These Chinese cases manifest as MH crisis. The clinical grading scale of diagnosis of MH may provide clues for clinical diagnosis. CHCT can also be used in confirming diagnosis of MH in Chinese cases though they have different genetic background from their western counterparts.

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Malignant hyperthermia (MH) is a potentially fatal disorder characterized by abnormal calcium homeostasis of skeletal muscles in response to some triggering agents, such as commonly used anesthetics (including volatile anesthetics and depolarizing muscle relaxants). MH is one of the most severe anesthesia-related complications associating with rapid progress and high mortality rate.¹⁻⁵ Typical features of MH episode can provide clues for clinical diagnosis, but diagnosis of MH is confirmed by *in vitro* caffeine-halothane contracture tests (CHCT) of skeletal muscle.⁶⁻¹⁴ Many studies on MH have been performed in western countries and more attentions are paid in China in recent years. However, the clinical diagnosis of all the reported MH cases is mainly based on clinical manifestations and blood biochemical tests in China. There are few researches on CHCT experimented in Chinese population. In this study, we applied the clinical grading scale of diagnosis of MH and the CHCT in the confirmation of MH in Chinese cases.

METHODS

Patients

Three cases of MH, from January 2005 to December 2007, were included. All patients (age 10–26 years,

male/female: 1/2) accepted general anesthesia for elective procedures, who had normal vital signs (temperature 36.0°C–37.0°C, heart rate 70–85 beats/min, and arterial blood pressure 120–130/75–95 mmHg). The biochemical indicators, including blood creatine kinase and myoglobin, were also within normal ranges. The patients had no family and personal history of neuromuscular diseases or malignant hyperthermia. Case 1 was scheduled for correction of congenital scoliosis. Anesthesia was induced with 5 mg midazolam, 0.1 mg fentanyl, 100 mg propofol and 5 mg vecuronium and maintained with 1%–2% isoflurane in 50% nitrous oxide/50% oxygen. Her vital signs remained stable until three hours after the induction, when the patient's pharyngeal temperature

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increased gradually to 40.0°C and heart rate reached to 130 beats/min. Rigidity of muscles of the whole body ensued, with end-tidal CO₂ increasing to 100 mmHg. Blood creatine kinase and myoglobin were significantly increased (maximum value of 3075 IU/L and 1460 ng/ml respectively). Sixty minutes after the life-saving interventions, the patient's pharyngeal temperature decreased to 36.5°C. She was transferred to the intensive care unit for further treatment. The postoperative period was uneventful and twenty days after the operation, the patient was discharged from the hospital with no further postoperative complications. Case 2 was scheduled for elective tonsillectomy. Anesthesia was induced with 10 mg etomidate, 100 mg propofol and 90 mg succinylcholine and maintained with intravenous 1% procaine infusion combined with 200 mg succinylcholine and 0.2 mg fentanyl in volume 250 ml. One hour after the induction, the patient's heart rate reached to 200 beats/min and arterial oxygen saturation decreased to 88%. Severe hypercarbia ensued, with end-tidal CO₂ rising to 180 mmHg. The patient's axillary temperature reached to 40.6°C and rigidity of extremities was noticed. Postoperative blood creatine kinase and myoglobin were significantly increased (maximum value of 2532 IU/L and 1500 ng/ml respectively). The patient was treated and transferred to the intensive care unit. The postoperative period was eventful and MH recurred three days after the operation. The patient remained in coma since then. Case 3 was scheduled for elective mandibular anaplasty. A total of 5 mg midazolam, 5 µg remifentanyl, 6 mg vecuronium and 100 mg propofol were administered to induce and maintained with 1%–2% isoflurane in 50% nitrous oxide/50% oxygen. One and half hours after the induction, the patient's pharyngeal temperature increased gradually and reached to 42.2°C, and heart rate reached to 140 beats/min. Severe hypercarbia ensued, with an increasing end-tidal CO₂ (up to 140 mmHg). The patients developed systematic muscle rigidity and her blood creatine kinase and myoglobin were significantly increased (maximum value of 49 000 IU/L and 79 856 ng/ml respectively). The patient died three days after the operation because of MH recurrence.

Clinical grading scale of MH

The clinical grading scale of diagnosis of MH was designed to estimate the qualitative likelihood of MH and predict MH susceptibility. Clinical indicators include rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement and rhabdomyolysis. There are additional indicators in case of a family history for MH. For each indicator 3–15 points are added to build a raw score, corresponding to a MH rank that describes the likelihood of MH in the suspected event.^{15,16}

Caffeine-halothane contracture test

After informed consent was obtained, a muscle biopsy of the femoral quadriceps was performed immediately at the onset of MH for each patient. The CHCT was carried out

according to the protocol of the North America Malignant Hyperthermia Group (NAMHG).⁴⁻⁸ In brief, after the length and wet weight of each muscle bundle was measured, single muscle strips were mounted vertically in the experimental bath perfused with carboxygenated (95% oxygen, 5% carbon dioxide) Krebs-Ringer's solution (NaCl 118.1 mmol/L; KCl 3.4 mmol/L; CaCl₂ 2.5 mmol/L; MgSO₄ 0.8 mmol/L; KH₂PO₄ 1.2 mmol/L; NaHCO₃ 25.0 mmol/L; Glucose 11.1 mmol/L) at 37°C, fixed to an isometric force transducer (pclAB-UE, China) and stimulated electrically using a supramaximal square wave with 1 ms intervals and a frequency of 0.2 Hz (pclAB-UE, China). After equilibration, caffeine (Sigma) was added at increasing concentrations of 0.5, 1.0, 2.0, 4.0, 8.0 and 32.0 mmol/L respectively at 4 minutes intervals (caffeine test). The 3% halothane (Sigma) was given to another muscle strips for 10 minutes (halothane test). Resting tension and twitch height of the muscle strips were recorded continuously by a digital recording system (pclAB-UE).

Diagnostic criteria

In the NAMHG protocol, a contracture of ≥ 0.3 g at a concentration of caffeine ≤ 2 mmol/L and/or a contracture of >0.7 g in the halothane test is considered pathological. MH susceptibility (MHS) is diagnosed if a pathological contracture appears in the halothane test, caffeine test or both. Malignant hyperthermia negative (MHN) is diagnosed if there is no pathological contracture in both the halothane and caffeine tests.⁴⁻⁶

RESULTS

Clinical grading scale of MH

The clinical grading scale of diagnosis of MH was 58, 54 and 58 in Cases 1, 2 and 3 respectively, all ranking grade D6 and representing almost certain malignant hyperthermia.

Caffeine-halothane contracture test

Although no contracture of >0.7 g in the halothane test was detected (Figure 1), a contracture of >0.3 g at caffeine 2 mmol/L in caffeine test of each cases is considered pathological and the patient was diagnosed as MH susceptibility according to the protocol of the NAMHG (Figure 2).

DISCUSSION

MH is a pharmacogenetic clinical syndrome that manifests as a hypermetabolic crisis when a susceptible individual is exposed to certain anesthetic triggering agents. Clinical signs include unexplained elevation of end-tidal CO₂, muscle rigidity, acidosis, tachycardia, tachypnea, hyperthermia, and evidence of rhabdomyolysis. The incidence of MH varies between different reports, ranging from 1 in 2000 to 1 in 15 000 in general anesthetics in children and from 1 in 20 000 to 1 in 26 000 in general anesthetics in adults. MH has received much attention in

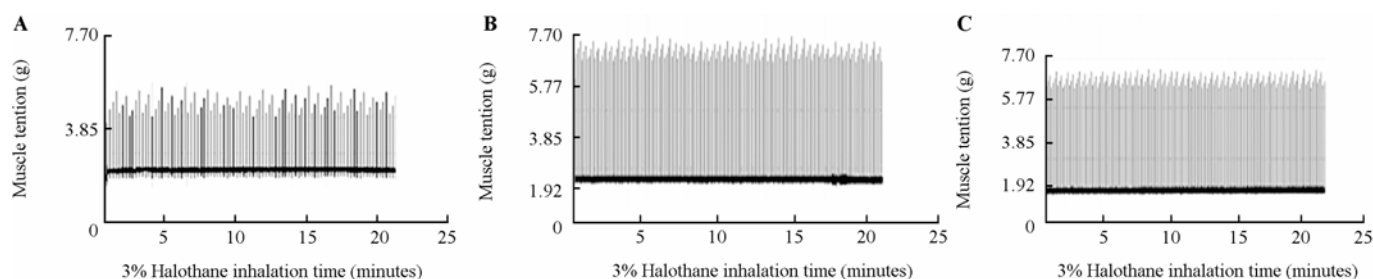


Figure 1. Results of halothane test. No contracture of >0.7 g in the halothane test was detected. **A:** Curve of halothane test in Case 1. **B:** Curve of halothane test in Case 2. **C:** Curve of halothane test in Case 3.

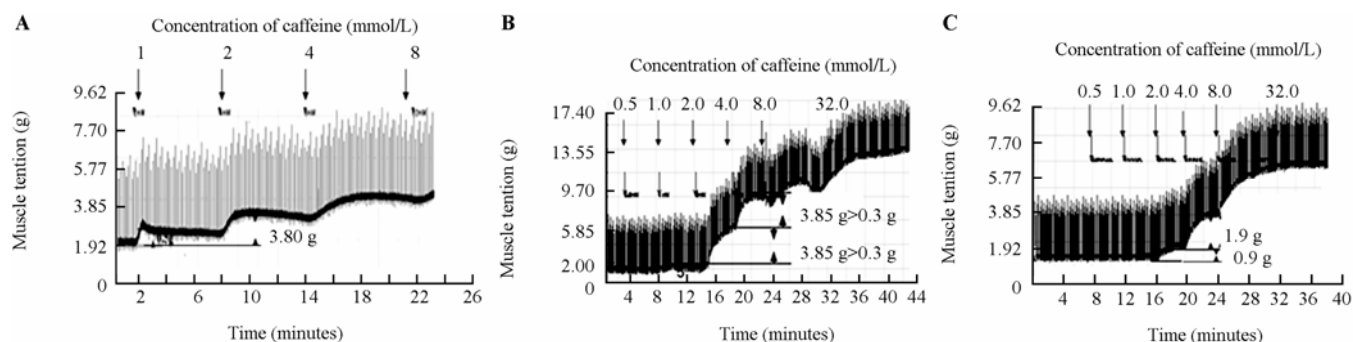


Figure 2. Results of caffeine test. **A:** Curve of caffeine test in Case 1. The contracture of 3.8 g (>0.3 g) at caffeine 2 mmol/L is considered pathological. **B:** Curve of caffeine test in Case 2. The contracture of 3.85 g (>0.3 g) at caffeine 2 mmol/L is considered pathological. **C:** Curve of caffeine test in Case 3. The contracture of 0.9 g (>0.3 g) at caffeine 2 mmol/L is considered pathological.

scientific literatures.^{1,2} From the first case report in 1960 until now, hundreds of studies have been conducted in western countries. The diagnosis of MH has evolved from subjective assumptions by family history and clinical diagnosis to more sophisticated laboratory testing.³⁻⁶

A multifactor MH clinical grading scale, comprising standardized clinical diagnostic criteria, was developed for classification of existing records and for application in new patients.^{15,16} This scale ranks the qualitative likelihood that an adverse anesthetic event represents MH event rank. The higher the score ranks, the more MH happens possibly, and *vice versa*. The MH clinical grading scale is recommended as an aid to the objective definition of this disease in western countries. Although the clinical grading scale allows some guidance in deciding whether a patient has MH susceptibility, it will be underestimated if the clinical data are insufficient. In addition, typical features of MH episode can provide clues for clinical diagnosis, but it is different in early clinical behaviors and when it manifests typically, it is hard to save the patient's life.

A genetic basis of MH was recognized in the early 1990s and complex genetic pathways have been demonstrated since then.^{2,3,17} More information of the genetics of MH is necessary to explore the exact pathological mechanisms involved in MH. A powerful diagnostic tool may be developed from human genome project (HGP). The advantages of genetic testing over the contracture test include noninvasiveness, lower cost, and the lack of morbidity of muscle biopsy. However, it cannot be used

as a screening test currently because of the low prevalence of MH in the general population. The genetic basis of MH susceptibility is still not fully understood. Genetic screening for common mutations might miss rare or new mutations, which is a reason why a negative test result would not exclude MH susceptibility. Obviously, genetic testing cannot replace the contracture test currently.

Major efforts have been made to find a noninvasive diagnostic test, but the CHCT of skeletal muscle strips, which has been the only means of patient screening since the last 30 years, is still the most definitive test for MH susceptibility.^{5,18,19} Moreover, CHCT is helpful for genetic research.

The NAMHG protocols test an *in vitro* contracture response of muscle fiber bundles from biopsy muscle to halothane and, in separate strips, to caffeine. The CHCT achieves high sensitivity (97%) and acceptable specificity (78%) when it is performed according to NAMHG protocol.⁴⁻⁸ A CHCT is performed on the patient or his or her parents if the patient is too young or has not survived the anesthetic event. If MH is confirmed by CHCT, there is a clinical responsibility to offer the CHCT to the relatives of the index case.

Until now, the CHCT is still the gold standard for determination of MHS, but there are few studies about it in China. By analyzing the literature in mainland China, we found that case reports of MH are scattered and tended to increase in China recently.²⁰ Most cases of MH

were diagnosed according to clinical manifestation only without the confirmation of the golden standard of diagnosis of MH-CHCT. Dantrolene was not available and the mortality rate is up to 73.5% in China. Early diagnosis and availability of dantrolene are essential to lower the mortality of MH in mainland China. Above all, studies on MH in mainland China should be enforced by establishing a laboratory diagnostic standard.

In the cases of this study, succinylcholine and sevoflurane had been identified as the trigger agents. All the patients presented typical manifestations of fulminant MH after anesthesia, such as dramatic increase in both end-tidal CO₂ and body temperature, muscle rigidity, metabolic acidosis and significant elevation of creatine kinase levels. According to the MH clinical grading scale, all the patients ranked grade D6, which represented almost certain MH.^{15,16} CHCT was applied in these cases to confirm the clinical diagnosis of MH. Because a pathological contracture was detected in caffeine contracture test, all the patients were diagnosed as MHS according to the protocol of the NAMHG though a halothane contracture test is negative.

Dantrolene is considered essential for the management of MH. As Chinese patients are rarely considered to be at risk of MH, dantrolene is not widely available in the mainland of China. We carried out promptly the following measures for the three cases: (1) discontinuing the triggering anesthetic (isoflurane and succinylcholine) and operation; (2) changing the entire anesthetic circuit; (3) hyperventilating with 100% oxygen at a flow of more than 10 L/min; (4) beginning aggressive cooling (ice packs, cooling blankets and cold IV fluids); (5) administering furosemide; and (6) giving 5% sodium bicarbonate according to blood gas analysis.

Aggressive management of the patient's temperature, attention to acidosis, and prompt termination of MH-triggering drugs resulted in a good outcome in Case 1. The patient 3 developed multi-organ dysfunction including renal and hepatic failure as well as serious rhabdomyolysis, acute respiratory distress syndrome and disseminated intravascular coagulation (DIC). A special problem of intensive care treatment is the management of severe hyperthermia. Lowering body temperature, however, may be a major clinical problem because hyperthermia is typically unresponsive to antipyretic agents while manual cooling proves difficult due to peripheral vasoconstriction.

Although properly treated, unfortunately, the patient of Case 2 could not recover and Case 3 died of the recurrent MH episode. Our experience suggests that dantrolene should be available for MH emergencies in China.^{21,22}

When patients are known to be MH susceptibility prior to surgery, an MH episode can easily be avoided by the use of safe non-triggering anesthetic agents. Elective anesthesia in patients with MH susceptibility should

avoid succinylcholine and halogenated inhalation anesthetics. The anesthesia machine should be carefully cleansed of vapor from halogenated agents (flushing the system with oxygen, use of fresh disposable anesthetic circuits, changing of reservoir bags and ventilation balloons). During anesthesia, monitoring of central body temperature, expired CO₂, blood pressure, blood gases analysis, creatine kinase, myoglobin, and immediate treatment with dantrolene are a prerequisite for anesthetizing MH susceptibles. Many experts believe that the mortality rate of MH can be significantly reduced by improving MH diagnosis and careful preparations.

MH susceptibility does exist in Chinese patients and MH episode will increase year by year with the general application of volatile anesthetics in China. MH is one of the most severe anesthesia-related complications with high mortality rate. Early diagnosis, which can lower the mortality rate, is fundamentally important. It is urgent to use successful experiences from other countries and improve the level of diagnosis and therapy for MH in China. The CHCT is the only validated test for diagnosing MH susceptibility and phenotyping MH susceptibility families in western countries. In our study we can conclude that the clinical grading scale of diagnosis of MH may provide clues for diagnosis, while CHCT can also be used in diagnosis of MH in Chinese cases, who have different genetic background with their western cousins. We suggest that this specialized diagnostic testing be used to diagnose and treat the disease and promote further research on MH in China.

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