

# Update in Anaesthesia

## Successful management of malignant hyperthermia without dantrolene in paediatric anaesthesia

Sami Menasri, Rabie Slimani, Nadia Grainat, Nejma Brinis, Haithem Bourenane and Yacine Zerizer

Correspondence: s.menasri@hotmail.fr

### KEY WORDS

Malignant hyperthermia, paediatric anaesthesia, dantrolene sodium

### ABSTRACT

Malignant hyperthermia is a rare inherited disorder that develops following exposure to volatile anaesthetic agents and depolarising muscle relaxants. The overall incidence of malignant hyperthermia during general anaesthesia is estimated to range from 1 in 5000 to 1 in 50,000–100,000 and the mortality rate is estimated to be < 5% in the presence of standard care.<sup>1,2</sup> In Algeria, this incidence is even lower because of the absence of the succinylcholine second triggering agent, but there is no centre where an in vitro caffeine–halothane contracture test is performed to confirm the diagnosis in suspected cases. The drug of choice for this condition, dantrolene, is not freely available in Algeria. We hereby report the case of a 7-year-old boy who had previously undergone uneventful general anaesthesia. He developed malignant hyperthermia and survived the condition despite the non-availability of dantrolene, emphasising the role of early detection and aggressive management in these cases. Survival without dantrolene remains exceptional, especially in paediatric cases (there are few cases in the recent literature).<sup>3,4</sup> This is probably the first case report of this disease from Algeria.

### INTRODUCTION

Malignant hyperthermia (MH) is a hypermetabolic response to volatile anaesthetic gases such as sevoflurane and the depolarising muscle relaxant succinylcholine, as a result of a pharmacogenetic disorder of skeletal muscle.<sup>5</sup> The incidence and prevalence of MH vary with age and gender. The incidence in adults is 1 in 50,000 and in children is

1 in 15,000.<sup>4</sup> It occurs more frequently in males than females.<sup>4,5</sup> The incidence of MH in Algeria may not be as low as expected, especially before the systematic use of capnography. Genetically, MH is an autosomal dominant condition.<sup>1,4</sup> The pathophysiology of MH involves altered sarcoplasmic reticulum calcium channel-gating kinetics.<sup>1</sup> The high level of calcium in sarcoplasmic reticulum results in aerobic metabolism, glycolysis and neutralisation of hydrogen ions and hydrolysis of high-energy phosphate compounds leading to acidosis, rigidity, altered permeability, hyperkalaemia and a rise in temperature. The first sign of MH under anaesthesia is the increase in end-tidal CO<sub>2</sub> exponentially. Early management of MH, strongly suspected on a clinical basis, could alter a patient's outcomes.<sup>6,7</sup>

### CASE DESCRIPTION

An active, healthy, 7-year-old boy weighing 22 kg was scheduled to undergo laparoscopic surgery for undescended left testicle under general anaesthesia. In the pre-anaesthetic examination, neither the patient nor his family had any history of a neuromuscular disease or a family history of anaesthetic complications. The patient received surgery for right ectopic testes at the age of 5 years under general anaesthesia using halothane, propofol and fentanyl and no significant complications occurred. Clinical examination detected a thoracic deformity (globular thorax) and the airway was Mallampati grade II. All routine hematological and biochemical investigations were found to be normal. In the operating room, an intravenous line was secured under inhalation anaesthesia (sevoflurane) and minimum basic monitoring of the patient was carried out [peripheral capillary oxygen saturation, non-invasive blood pressure, electrocardiography and end-tidal carbon dioxide (CO<sub>2</sub>)]. Temperature is not routinely monitored for such surgery; the temperature probe was inserted only during crisis management. Anaesthesia was induced using propofol, fentanyl

**Sami Menasri**  
Batna University Hospital  
Batna  
Algeria

**Rabie Slimani**  
Batna University Hospital  
Batna  
Algeria

**Nadia Grainat**  
Batna University Hospital  
Batna  
Algeria

**Nejma Brinis**  
Batna University Hospital  
Batna  
Algeria

**Haithem Bourenane**  
Batna University Hospital  
Batna  
Algeria

**Yacine Zerizer**  
Batna University Hospital  
Batna  
Algeria

and rocuronium and the patient was ventilated with oxygen and sevoflurane; the patient was intubated with a cuffed endotracheal tube and connected to the ventilator. Anaesthesia was maintained with 50% oxygen–50% nitrous oxide and sevoflurane with boluses of rocuronium. After 75 minutes, a rising trend in end-tidal CO<sub>2</sub> was noticed at 54 mmHg, with lack of relaxation signalled by the surgeon; bilateral breath sounds without wheezing were maintained and measured. Temperature was 36.2°C. Initially, adjustment in minute ventilation, circuit check and reinjection of rocuronium was carried out, but the end-tidal CO<sub>2</sub> continued to rise, with the maximum rise of end-tidal CO<sub>2</sub> to 80 mmHg. There was an associated rise in temperature, with a maximum reading of 38.3°C recorded by a nasopharyngeal probe. The surgeons reported that muscle tension was still very high and the lower extremities remained rigid and warm to touch. The patient also had an elevated heart rate and blood pressure, with maximum readings of 130 beats/minute and 135 mmHg, respectively. Suspecting MH, sevoflurane was stopped, propofol infusion was started and the patient was ventilated with 100% oxygen through a new anaesthetic circuit using higher gas flows and higher minute ventilation. The surgeon was informed and asked to expedite surgery. Active cooling was started with ice-cold saline intravenously. A urinary catheter was inserted to check for diuresis. The results of tests carried out intraoperatively were as follows: creatinine kinase 3905 IU/l, sodium 140 mEq/l, potassium 4.4 mEq/l, blood urea 0.3 g/l, creatinine 8 mg/l. A blood gas sample was unavailable at this time. The drug of choice for MH, dantrolene, could not be used as it was not available in our hospital. With active cooling, the temperature decreased significantly and normalised. With high minute ventilation end-tidal CO<sub>2</sub> was also controlled. Surgery was completed without severe haemodynamic changes and pulmonary complications; the patient recovered and was extubated successfully in the operating room once the end-tidal CO<sub>2</sub> and temperature returned to normal and the patient achieved criteria for extubation. The patient was carefully monitored and investigated in the postoperative period and a severe rise in creatine phosphokinase was recorded at 24 hours. The rest of the laboratory work-up was normal. There were no active complaints from the patient except for muscle rigidity and body aches. His creatinine phosphokinase levels are shown in Table 1. To avoid rhabdomyolysis-associated renal injury he received volume loading. The patient was discharged on the eighth day. The patient and his attendants were made aware of the suspected diagnosis of MH and the risks of recurrence in the patient and other family members.

## DISCUSSION

We made the diagnosis of MH on the basis of clinical features. As demonstrated in this case, any patient may develop MH during or shortly after an anaesthetic procedure when trigger agents are used, and this may occur even in patients who have had uneventful anaesthesia previously.<sup>8</sup> It has been estimated that on average three anaesthetics are required before an adverse event is triggered in an MH-susceptible patient.<sup>1</sup> Although a detailed anaesthetic history is an important part of the perioperative assessment, 21% of MH

**Table 1.** Creatinine phosphokinase (CPK) levels in the patient

Time period	CPK (IU/l)
Operative day	3904
First postoperative day	16,000
Second postoperative day	13,214
Fourth postoperative day	10,100
Sixth postoperative day	1150
Seventh postoperative day	160

patients report previous uneventful anaesthesia and 75% report a negative family history.<sup>9</sup> The clinical presentations of MH are diverse, ranging from mild to moderate symptoms to life-threatening crises caused by severe rhabdomyolysis.<sup>8</sup> This was a typical case of MH because of the high level of end-tidal CO<sub>2</sub>, increase in temperature and muscle rigidity. In children, sinus tachycardia and hypercapnia have been shown to be the two most reliable early clinical signs.<sup>10</sup> Fever, hyperkalaemia and elevated creatine kinase are late signs and their absence does not exclude the diagnosis.<sup>11</sup> The moderate clinical presentation was the result of the early recognition of non-specific clinical signs of MH and the initiation of rapid appropriate treatment.

The severity of MH also depends on the dose of triggering agents given to the patient.<sup>12</sup> Sevoflurane is thought to be a less potent trigger, with there often being a more gradual onset of MH or the occurrence of an incomplete form of MH.<sup>11</sup> A clinical grading scale is considered a useful tool for the detection of MH.<sup>13</sup> This numerical assessment tool, developed by Larach *et al.*,<sup>14</sup> can be used to indicate the likelihood that an adverse anaesthetic event represents MH. Scores of 35–49 suggest that MH is very likely and scores of ≥ 50 indicate an almost certain probability of MH. Our patient had a calculated raw score of 63 (Table 2), placing him in the ‘almost certain’ range for an MH event.<sup>13</sup>

Other causes of the hypermetabolic crisis were ruled out as the patient had a normal thyroid function test, was not on any antipsychotic drugs and had no history suggestive of phaeochromocytoma. Overall, the anesthetist needs to apply good clinical judgement and have a strong suspicion for MH if end-tidal CO<sub>2</sub> continues to rise

**Table 2.** MH clinical presentation score: likelihood that an adverse anaesthetic event represents MH

Parameter	Score (points)
Rigidity (generalised muscular rigidity)	15
Muscle breakdown (elevated creatine kinase concentration > 10,000 IU/l)	15
Respiratory acidosis (PaCO <sub>2</sub> > 60 mmHg with appropriately controlled ventilation)	15
Temperature increase (inappropriately rapid increase in temperature, in the anesthetist’s judgement)	15
Cardiac involvement (inappropriate sinus tachycardia)	3

despite adjusted minute ventilation. This case illustrates the value of capnography monitoring for the timely recognition of the condition, which is key to patient survival. Some cases of MH have probably not been diagnosed because of a lack of this essential monitoring, particularly in some peripheral centres and in private practice in Algeria. The early suspicion of MH and rapid appropriate treatment led to a favourable prognosis of this MH crisis.<sup>8</sup> In addition to being a specific treatment for MH, dantrolene can decrease the mortality rate;<sup>1</sup> other immediate interventions include stopping the trigger agents, changing to total intravenous anaesthesia and removing the volatile anaesthesia from the anaesthesia machine. Changing the breathing circuits and hyperventilating with 100% oxygen at a maximum fresh gas flow will help remove the triggering agent and accumulated CO<sub>2</sub> as well as compensate for the increased metabolic oxygen requirement. Cooling techniques such as gastric lavage or placing ice internally and externally can help lower the core temperature. Using ice-cold intravenous fluids will also rapidly decrease the core temperature, as in our case.

The successful outcome in this case without administration of dantrolene was the result of the early diagnosis and intervention by multiple trained personnel. Cases of survival without dantrolene have been reported in paediatric practice. Continued monitoring is of particular importance as the recurrence of symptoms has been reported in 14.4% of paediatric patients after the initial treatment.<sup>10</sup> Thus, fluid infusion was employed to prevent acute renal failure in our case.<sup>11</sup> For a definitive diagnosis of MH an in vitro caffeine–halothane contracture test is used.<sup>15</sup> This test is not available in Algeria and so we relied on the clinical grading scale.<sup>13</sup> High MH scores are significantly correlated with the caffeine–halothane contracture test.<sup>16</sup> DNA testing is now used routinely for diagnosis before muscle biopsy when a familial *RYR1* mutation is known.<sup>17</sup> Genetic testing for MH is not available in Algeria.

## CONCLUSION

This case highlights the importance of clinical vigilance for this rare condition. It may be encountered only once in an anesthetist's career. We strongly support the monitoring of capnography and temperature during anaesthesia as they are the most common clinical signs of acute MH. Anaesthesia providers should have a high level of suspicion for an MH event; early awareness and proper management including initial and symptomatic treatment is crucially important, and dantrolene, which remains the gold standard for treatment, should be made available.

## REFERENCES

- Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet J Rare Dis* 2007; **2**: 21.
- Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. *Anesthesiology* 2009; **110**: 89–94.
- Hopkins PM. Malignant hyperthermia: advances in clinical management and diagnosis. *Br J Anaesth* 2000; **85**: 118–28.
- Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001–2005. *Anesth Analg* 2009; **109**: 1162–6.
- Sumitani M, Uchida K, Yasunaga H, Horiguchi H, Kusakabe Y, Matsuda S et al. Prevalence of malignant hyperthermia and relationship with anesthetics in Japan: data from the diagnosis procedure combination database. *Anesthesiology* 2011; **114**: 84–90.
- Monnier N, Kozak-Ribbens G, Krivacic-Horber R, Nivoche Y, Qi D, Kraev N et al. Correlations between genotype and pharmacological, histological, functional, and clinical phenotypes in malignant hyperthermia susceptibility. *Hum Mutat* 2005; **26**: 413–25.
- Torpy JM, Lynam C, Glass RM. Malignant hyperthermia. *JAMA* 2005; **293**: 2958.
- Schneiderbanger D, Johannsen S, Roewer N, Schuster F. Management of malignant hyperthermia: diagnosis and treatment. *Ther Clin Risk Manag* 2014; **10**: 355–62.
- Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. *Anesth Analg* 1993; **77**: 297–304.
- Nelson P, Litman RS. Malignant hyperthermia in children: an analysis of the North American malignant hyperthermia registry. *Anesth Analg* 2014; **118**: 369–74.
- Glahn KP, Ellis FR, Halsall PJ. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth* 2010; **105**: 417–20.
- Hopkins PM. Malignant hyperthermia: pharmacology of triggering. *Br J Anaesth* 2011; **107**: 48–56.
- Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994; **80**: 771–9.
- Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg* 2010; **110**: 498–507.
- Gupta PK, Hopkins PM. Editorial. Malignant hyperthermia in India. *Anesthesia* 2010; **65**: 1059–68.
- Studio RT, Cunha LB, Carmo PL, Matos AR, Trachez MM, Cardoso LA et al. Use of the caffeine halothane contracture test for the diagnosis of malignant hyperthermia in Brazil. *Braz J Med Biol Res* 2010; **43**: 549–56.
- Urwiler A, Deufel T, McCarthy T, West S, European Malignant Hyperthermia Group. Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. *Br J Anaesth* 2001; **86**: 283–7.