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# Malignant hyperthermia triggered by isoflurane and suxamethonium in a patient who underwent apparently uneventful halothane anesthesia previously: a case report

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## Introduction

Malignant hyperthermia (MH) is a syndrome of skeletal muscle hypermetabolism. MH remains a serious and potentially life-threatening complication of anesthesia. MH occurs sporadically in Japan and is of autosomal dominant inheritance [1]. The occurrence of MH cannot be explained by gene malfunction alone, because 20.9% of MH-susceptible patients have previously undergone uneventful anesthesia [2]. We report a case of fulminant MH caused by isoflurane and suxamethonium, but not by halothane anesthesia. Muscle biopsies for $Ca^{2+}$-induced $Ca^{2+}$ release (CICR) of the patient's mother, sister, and brother were positive.

## Case report

A 15-year-old boy weighing 45 kg who had essential pied creux and right tenontoplasty of the plater muscle tendon was scheduled at Hirosaki Memorial Hospital. The patient had undergone the same procedure on the left foot under general anesthesia at 11 years of age. Anesthesia was induced with intravenous thiopental 200 mg without suxamethonium and maintained with halothane. Tachycardia (maximum 160 bpm) was observed during anesthesia, but no other signs of MH were observed. His past medical history was otherwise unremarkable. Preoperatively, we had no information about a family history of MH. He was premedicated with 10 mg of oral diazepam 60 min before the start of anesthesia. Anesthesia was induced with intravenous thiopental 250 mg, and tracheal intubation was facilitated by 40 mg of intravenous suxamethonium. He developed jaw muscle rigidity after administration of suxamethonium but was intubated with little difficulty. Anesthesia was maintained with droperidol 2.5 mg and pentazocine 30 mg in combination with 70% nitrous oxide and 30% oxygen under assisted ventilation. The blood pressure and heart rate were 110/65 mmHg and 70 bpm 30 min after administration of suxamethonium. He did not develop muscle rigidity. The nasopharyngeal temperature was elevated from 36.0°C to 36.6°C 30 min after the start of anesthesia. Eighty minutes after the start of anesthesia, as blood pressure and heart rate increased to 145/65 mmHg and 85 bpm, 7.5 mg pentazocine and 0.5% isoflurane were given because the depth of anesthesia was considered insufficient. Fifteen minutes after the start of isoflurane administration, the nasopharyngeal temperature increased to 38.4°C and end-tidal $CO_2$ was elevated to 80.0 mmHg. The inhalation of isoflurane was immediately discontinued, vigorous cooling procedures with ice packs were started, and 1000 ml of iced lactated Ringer's solution was given. The anesthesia machine was changed and hyperventilation was continued. Laboratory data 170 min after the start of anesthesia were serum creatine phosphokinase (CK) 307 IU·l$^{-1}$ and serum $K^+$ 4.7 mEq·l$^{-1}$. Arterial gas values ($FiO_2$ 0.3) were Ph 7.038, $PCO_2$ 96.0 mmHg, $PO_2$ 95.4 mmHg, and base excess −10.0 mEq·l$^{-1}$. The body temperature rose to a maximum of 40.8°C. $SpO_2$ at the left first finger decreased to a minimum of 93%. Three hours and thirty-five minutes after the start of anesthesia, as the temperature decreased to 38.4°C and arterial gas values were Ph 7.330, $PCO_2$ 42.6 mmHg, and $PO_2$ 450.6 mmHg ($FiO_2$ 1.0), the endotracheal tube was removed. Sixty minutes after extubation, arterial blood analysis showed Ph 7.352, $PaCO_2$ 42.3 mmHg, $PO_2$

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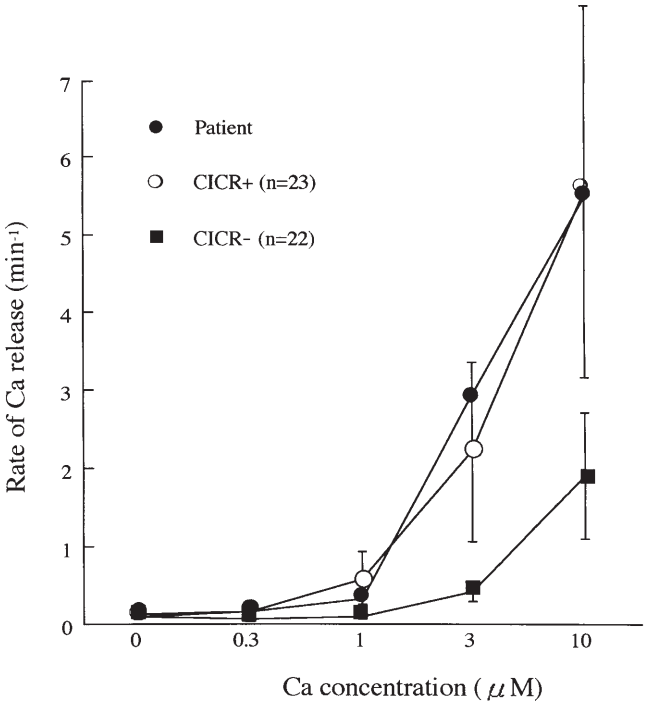


**Fig. 1.** $Ca^{2+}$-induced $Ca^{2+}$ release test (*CICR*) in the patient. The data were provided by Keiko Mukaida, Department of Anesthesiology, Hiroshima University. This patient was judged to be susceptible, because his CICR was higher than mean + 2 × SD of CICR of patients who did not develop MH. The CICR+ group consists of patients who developed fulminant MH. The CICR− group consists of patients who did not develop MH. The rate of Ca release is expressed by the equation $r = -\ln (Ca_t) \cdot (Ca_i)^{-1} \cdot t^{-1}$ (min), where $Ca_t$ is the amount of $Ca^{2+}$ in the SR after $t$ minutes of stimulation with exogenous $Ca^{2+}$, $Ca_i$ is the initial amount of $Ca^{2+}$ in the sarcoplasmic reticulum before stimulation with $Ca^{2+}$, $r$ is the rate constant, and $t$ is the duration in minutes of stimulation at a certain pCa. $n$ is the number of subjects tested. Data were expressed as means ± SD

340.7 mmHg (100% $O_2$ 6l), and base excess $-2.2\,mEq \cdot l^{-1}$. Three hours after extubation, serum CK was $5287\,IU \cdot l^{-1}$ and urine myoglobin was over $500\,ng \cdot ml^{-1}$. Urine output was 280 ml during anesthesia and was maintained at more than $50\,ml \cdot h^{-1}$ after surgery. The further course of recovery was uneventful.

A muscle biopsy was scheduled under local anesthesia with 2% procaine two months after the MH episode. The patient did not show any signs of a raised metabolic state. The axilliary temperature indicated a maximum of 36.7°C. The results of arterial blood gas analyses were within normal limits. His CICR test, which is the test for the potentiated Ca-induced $Ca^{2+}$ release function of the sarcoplasmic reticulum and has high sensitivity for malignant hyperthermia [3], was positive (Fig. 1).

Recently we obtained information that the patient's cousin developed fulminant MH without a fatal result and his aunt had a fever of more than 40°C during general anesthesia, but further information was not available. Muscle biopsies for CICR were performed for his family in Aomori Rosai Hospital. His mother, sister, and brother were classified as MH-susceptible individuals.

## Discussion

MH can be triggered by volatile anesthetics and suxamethonium. This syndrome is characterized by arrhythmias, muscle regidity, metabolic and respiratory acidosis, and acute elevation of the body temperature. In this patient, a combination of hyperthermia, hypercarbia, acidosis, base deficit, myoglobinuria, and elevated CK levels supports the clinical diagnosis of MH as proposed by Larach et al. [4]. The CICR test for this patient was positive. The pathophysiology of MH is related to the malfunction of intracellular $Ca^{2+}$ homeostasis in skeletal muscle [5]. Abnormality in the $Ca^{2+}$ release channel (ryanodine receptor) of the sarcoplasmic reticulum is considered the cause of MH [6]. Susceptibility to MH may be caused by genetic defects, and mutations in the ryanodine receptor gene have been identified [7]. However, 3%–75% of patients who developed fulminant MH did not have genetic defects and mutations in the ryanodine receptor gene [8]. Accordingly, the occurrence of MH appears to be associated not only with gene malfunction, but also with other factors. Strazis et al. reported that, of 503 patients with MH, at least 20.9% had received previous uneventful anesthesia [2]. Britt demonstrated that a previous history of uneventful anesthesia does not rule out the possibility of future malignant hyperthermia [1]. According to Ording, MH is classified as fulminant or abortive according to the body temperature [9]. Abortive MH shows some symptoms of muscle rigidity, tachycardia, arrhythmias, hypoxia, metabolic and respiratory acidosis, myoglobinuria, and elevated CK without acute elevation of the body temperature of more than 40°C, or 0.5°C in 15 min [9]. Our patient would be classified as having abortive MH in the previous anesthesia. Abortive MH may progress to fulminant MH if the patient is not be treated or the duration of anesthesia is long. Since the duration of the previous anesthesia was 60 min, the duration of anesthesia may be associated with the occurrence of fulminant MH, but the use of suxamethonium appears to be a more important factor. On the other hand, since an enhanced CICR was observed in only a few patients with abortive MH, abortive MH may be different from fulminant MH [10]. Clarification of the relationship between fulminant and abortive MH may lead to an explanation for the different courses of the two anesthesias in this patient.

Both isoflurane and halothane are triggering drugs for MH. Reed and Strobel reported that caffeine-induced muscle contractures induced by halothane are greater than those induced by either enflurane or isoflurane in animals [11]. By using muscle from MH-susceptible patients, Britt et al. also demonstrated that isoflurane is less potent than halothane at inducing caffeine-induced muscle contractures [12]. These reports indicate that halothane induces MH more easily than isoflurane. In previous anesthesia in this patient, suxamethonium was not used. Suxamethonium is also a triggering drug of MH [13]. The patient developed masseter muscle rigidity (MMR) after administration of suxamethonium. MMR occurs in about 1% of children after administration of halothane and suxamethonium [14] and is often considered a warning sign of MH. Rosenberg and Fletcher found the coincidence of susceptibility to MMR and MH to be 51% [15]. However, Littleford et al. pointed out that even if MMR occurs in children, it is safe to continue anesthesia and surgery while monitoring carefully for signs of hypermetabolism [16]. Our patient developed jaw muscle rigidity after suxamethonium administration, but he did not develop rapid elevation of body temperature and increase in end-expiratory concentrations of carbon dioxide. Therefore, the anesthesia was continued. Though the MH occurred about 60 min after suxamethonium administration, intracellular $Ca^{2+}$ metabolism altered by suxamethonium might be enhanced by isoflurane inhalation. The increase in heart rate and blood pressure may be related to the change in $Ca^{2+}$ metabolism. Thus, suxamethonium also appears to be partly associated with the occurrence of MH in this case. On the other hand, cases of MH involving non-depolarizing muscle relaxants have been described [17], but the drugs do not seem to be directly involved in the cause of MH. There are very few cases of MH associated with intravenous anesthetics. Vecuronium, pentazocine, and droperidol do not appear to be associated with the occurrence of MH [2,17].

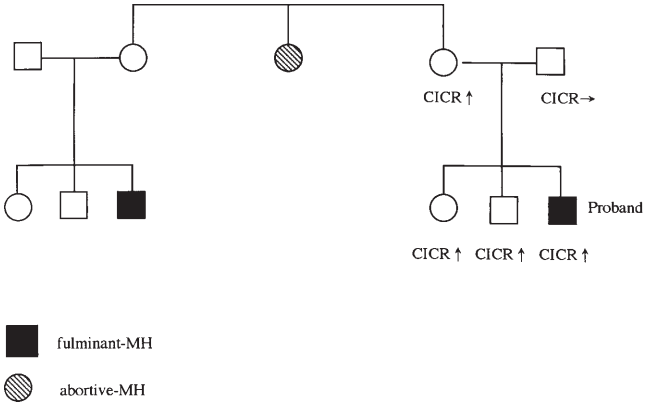


**Fig. 2.** $Ca^{2+}$-induced $Ca^{2+}$ release test for the patient's family

Patients with musculoskeletal defects are likely to develop MH [13,18]. Musculoskeletal surgical procedures are associated with MH [19]. Forty percent [20] or 7.8% [2] of MH cases are reported to be associated with musculoskeletal congenital defects. Such a large differ-

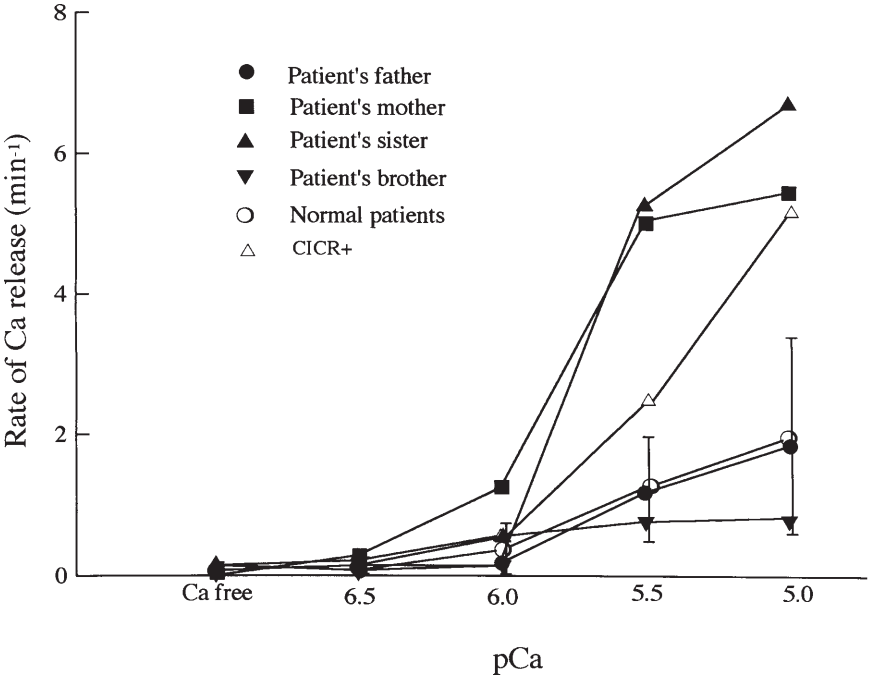


**Fig. 3.** $Ca^{2+}$-induced $Ca^{2+}$ release test for the patient's family. The CICR− group consists of patients who did not develop MH. Data from normal patients were provided by Yasuko Ichihara, Department of Anesthesiology, Toho University School of Medicine, and are expressed as means ± SD

ence in incidence seems to be a result of including different kinds of musculoskeletal disease. All patients with musculoskeletal defects do not appear to be at increased risk for MH. Pied creux is caused by neuromuscular diseases such as muscular dystrophy, Charcot-Marie-Tooth disease, polyneuritis, poliomyelitis, and Friedrich's ataxia [21], but in this case, a specific cause or neurologic deficit could not be found. We could not find any reports of MH in patients with pied creux, and it is unclear whether the disease is classified as a musculoskeletal defect. Children under 15 years of age comprise 52.1% of all MH cases, but the association between musculoskeletal disease and MH is independent of age [2]. Further study of this issue is mandatory.

Treatment of MH aims to reduce body temperature by applying external and internal cooling and to control biochemical disturbances, acidosis, and hyperkalemia. Dantrolene sodium is thought to be effective in the management of malignant hyperthermia by preventing calcium release from the sacroplasmic reticulum [22]. It was not used in the case we describe because it was not stocked in the hospital.

Postoperatively, we checked the family history and examined CICR for the petient's father, mother, sister, and brother. His mother's nephew had fulminant MH at 8 years of age, and his aunt had abortive MH at 24 years of age. Both survived the episodes. The CICR of his mother, sister, and brother was positive. Since MH is suggested to be of autosomal dominant inheritance [1], his mother's family will include the other MH-susceptible individuals. Active investigation of MH-susceptible family members will lead to the prediction and prevention of MH.

We have reported our experience of a case with hereditary MH. The patient had MH during isoflurane anesthesia but not during previous halothane anesthesia. The occurrence of MH in this patient might have been triggered by a combination of isoflurane and suxamethonium.

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