Suspected Malignant Hyperthermia During Sevoflurane Anesthesia

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Malignant hyperthermia is a rare anesthetic-related disorder. We present a case with unusual presentation. A boy aged 3 years and 9 months who was scheduled for Hotz's operation presented normally before the operation. Anesthesia was induced by atropine, thiopental and sevoflurane. Trachea intubation was facilitated by succinylcholine. Jaw stiffness was first noted although trachea was intubated without difficulty. The following tachycardia, hypercapnia and hyperthermia led to the diagnosis of malignant hyperthermia. Symptoms were relieved dramatically after the discontinuation of sevoflurane. Molecular genetic testing identified a novel ryanodine receptor (*RYR1*) mutation in exon 39, which confirmed malignant hyperthermia susceptibility in this patient. [*J Chin Med Assoc* 2007;70(11):507–510]

Key Words: general anesthesia, malignant hyperthermia, sevoflurane, succinylcholine

Introduction

Malignant hyperthermia is a rare anesthetic-related disorder, the clinical features of which are tachycardia and hypercapnia followed by hyperthermia.[1] The unusual increase in body temperature immediately after the induction of general anesthesia in our case may be due to the combined usage of succinylcholine and sevoflurane. Molecular genetic testing in this patient identified a novel ryanodine receptor (*RYR1*) mutation.

Case Report

A boy aged 3 years and 9 months was scheduled for Hotz's operation for entropion of both eyes under general anesthesia. He had never been anesthetized previously, and there was no known family history of malignant hyperthermia or muscle disease. Routine preoperative physical and laboratory examinations were normal, and there were no signs of recent infection. On arrival in the operating room, his body temperature was 36.8°C, heart rate was 89 bpm and weight was 16 kg.

Anesthesia was induced with 8% sevoflurane in 100% oxygen 5 L/min. After the intravenous line was set up, atropine 0.2 mg, thiopental 75 mg and succinylcholine 20 mg were administered. The anesthesiologist noted jaw stiffness when attempting tracheal intubation, and in the meantime, the patient's heart rate had risen to 155 bpm. Tracrium 8 mg was given to facilitate tracheal intubation and the trachea was intubated by Trachlight™. During the anesthesia procedure, an electrocardiogram, pulse oximeter and noninvasive blood pressure monitor were used. A nasopharyngeal temperature monitor and end-tidal CO_2 monitor were used after the patient's trachea was intubated. Anesthesia was maintained with 5% sevoflurane in 100% oxygen.

The end-tidal CO_2 (P_{ET} CO_2) was 69 mmHg when the endotracheal tube was first connected to the breathing circuit. This was managed by hyperventilation. However, despite our efforts, P_{ET} CO_2 gradually rose to 75 mmHg. Meanwhile, the patient's body temperature rapidly increased after general anesthesia was induced, from 36.8°C to 38.6°C in only 30 minutes.

Tachycardia, hypercapnia and rising body temperature were clues that pointed towards malignant hyperthermia. Sevoflurane was discontinued 30 minutes after anesthesia induction and anesthesia was then maintained with fentanyl and midazolam. At the same time, we changed the breathing circuit and soda lime and the

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fresh gas flow rate was increased to prevent rebreathing. The patient was uncovered to facilitate cooling. It was ensured that dantrolene was on hand.

Blood gas analysis revealed respiratory acidosis without hypoxemia (pH 7.239, PaO_2 575.3 mmHg, $PaCO_2$ 64 mmHg, HCO_3 27.6 mmol/L and BE –0.6 mmol/L). Plasma potassium level was 4.8 mmol/L. After discontinuation and washout of sevoflurane, P_{ET} CO_2 dropped dramatically and body temperature also decreased (Figures 1 and 2). As the fever subsided, dantrolene was not used. Two hours after the induction of general anesthesia, P_{ET} CO_2 had dropped to 34 mmHg and body temperature was 37.2°C. The patient was extubated in the operating room after recovering consciousness, and was then transferred to the pediatric intensive care unit (PICU) for further monitoring and management.

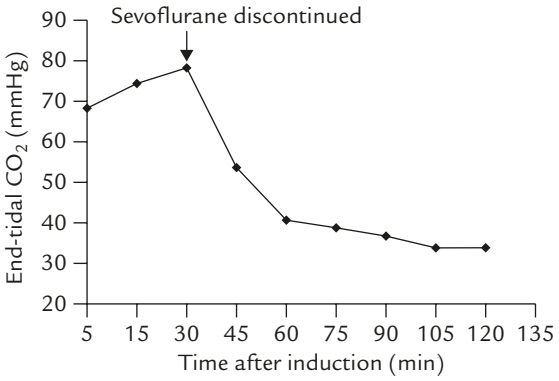

Figure 1. Change in end-tidal CO_2 following anesthetic induction.

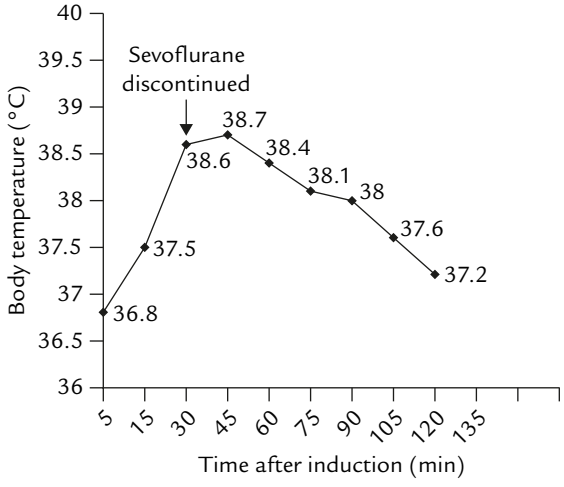

Figure 2. Change in body temperature following anesthetic induction.

In the PICU, the patient was hydrated and urine amount and urine pH were monitored and the urine alkalized if indicated. Serum creatine kinase level increased from 1,504 U/L (7-fold the normal level) during anesthesia to 27,100 U/L 24 hours after induction and returned to normal 5 days later. Serum myoglobin level was 4,000 μg/L (normal < 90 μg/L) during anesthesia and dropped to 467 μg/L 1 day later. Renal function was preserved; no dark-colored urine was produced. The patient recovered smoothly without complications.

After a thorough discussion with his parents, we sent a blood sample from the patient to the National Taiwan University Hospital for molecular genetic testing. The patient was found to be carrying a mutation in exon 39 of the ryanodine receptor gene (Figure 3); this mutation was Gly2130Arg. Molecular genetic testing of the patient's close relatives was also suggested to prevent catastrophe in the future.

Discussion

Malignant hyperthermia is a rare anesthetic-related disorder that is characterized by a hypermetabolic status, which occurs in patients with a genetic susceptibility caused by mutations in calcium channel proteins (ryanodine receptor, *RYR1*) or other genes.

It is known that all volatile anesthetics and succinylcholine may trigger malignant hyperthermia.[2] Sevoflurane is a less potent trigger, often with a more gradual onset or incomplete form of malignant hyperthermia.[2–5] But such was not the situation in this case. Our patient was a healthy boy with no family history

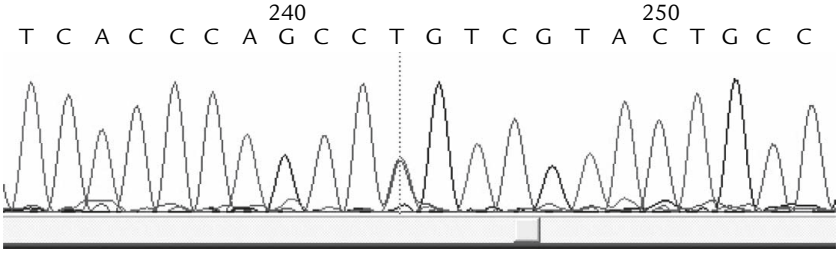

Figure 3. DNA sequencing was performed to identify the nucleotide mutation. The patient was carrying a *RYR1* mutation in exon 39. The mutation was Gly2130Arg.

of muscular dystrophy or other congenital disorders. Trismus after the induction of anesthesia was the first sign of malignant hyperthermia, followed by immediate hypercapnia and an immediate rise in body temperature (1.8°C within 30 minutes after the induction of general anesthesia), which are unusual in sevoflurane-induced malignant hyperthermia. A dramatic reduction in end-tidal CO_2 concentration and no further increase in body temperature after discontinuation of sevoflurane were noted (Figures 1 and 2). This strong correlation between sevoflurane and the clinical features of malignant hyperthermia indicated that sevoflurane was the most likely trigger agent in this patient. There are 2 possible explanations for the quick onset of symptoms after exposure to sevoflurane. First, sevoflurane was administrated combined with succinylcholine, which is also a trigger agent of malignant hyperthermia. Second, genetic background possibly accounts for the different clinical presentations among those susceptible to malignant hyperthermia.

There are disorders that mimic malignant hyperthermia, such as hyperthyroidism, neuroleptic malignant syndrome, sepsis and pheochromocytoma. Our patient had no medical history, and no signs of infection, unexplained hypertension or abnormal metabolism before the operation. None of these disorders offers a good explanation for why hypercapnia and hyperthermia correlated with the use of sevoflurane.

The early detection of malignant hyperthermia in our case may be attributed to vigilant and thorough perioperative monitoring. The major factors predicting the outcome of malignant hyperthermia are early diagnosis and rapid treatment.[1] A survey on the prevention and treatment of malignant hyperthermia in Taiwan was carried out by Yip and his colleagues.[6] In their report, the mortality rate of malignant hyperthermia in Taiwan was shown to be higher than those in North America and Europe (28% *vs.* 10%), a fact that the report blamed on incomprehensive intraoperative monitoring systems and a lack of dantrolene in many hospitals.

The gold standard to determine malignant hyperthermia susceptibility is the caffeine-halothane contracture test (CHCT). However, this test is not widely available. For those who do not have access to CHCT, the diagnosis can only be made by clinical presentation with the help of a clinical grading scale for malignant hyperthermia introduced by Larach and colleagues in 1994.[7] Our patient scored: (I) masseter spasm shortly following succinylcholine administration (15 points); (II) elevated creatine kinase >20,000 IU after anesthesia that included succinylcholine (15 points); (III) P_{ET} CO_2 >55 mmHg with appropriately controlled ventilation (15 points); (IV) inappropriately rapid increase in temperature (15 points); (V) inappropriate sinus tachycardia (3 points); and (VI) arterial pH <7.25 (10 points). The total score was 73 and ranked the patient as D6 — almost certain.

Studies have identified mutations within the ryanodine receptor (*RYR1*) gene and other genes as being responsible for malignant hyperthermia susceptibility, and many *RYR1* mutations have been described as being associated with malignant hyperthermia. The *RYR1* mutation identified in this patient (Gly2130Arg) has not been previously reported, and the location is within the mutation hot regions.[8] Gly2130Arg is evolutionally conserved in multiple animal species. Furthermore, this *RYR1* mutation was not detected in 50 normal subjects in Taiwan.[9] Therefore, it is highly likely that the mutation is responsible for malignant hyperthermia.

A study by Girard et al found a 50% chance of reliably confirming malignant hyperthermia susceptibility by noninvasive molecular genetic testing in families with known malignant hyperthermia mutations.[10] The negative predictive value of genetic testing was 0.95 while the value of CHCT was 0.78.[8,10] The low sensitivity (25%) of genetic testing should improve after more mutations are identified. At present, in places where CHCT is not available, such as in Taiwan, genetic testing for known mutations is an alternative way of confirming malignant hyperthermia susceptibility and preventing future catastrophe.[9]

Here, we have presented a case with immediate hypercapnia and a rapid rise in body temperature after exposure to succinylcholine and sevoflurane. The patient was found to be carrying a *RYR1* mutation. We attribute the good outcome of our patient to early diagnosis and adequate management. Vigilant and close perioperative monitoring is the key to early detection. Molecular genetic testing is an alternative way of confirming malignant hyperthermia susceptibility.

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