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Case Report

Malignant hyperthermia in a 4-year-old girl during anesthesia induction with sevoflurane and succinylcholine for congenital ptosis surgery

Fehmi Ferhi [a,*]; Leïla Dardour [b]; Amel Tej [c]; Raoudha Kebaili [c]; Sarra M'aaref [a]; Khaled Ben Jazia [a]

Abstract

Malignant hyperthermia (MH) is a rare pharmacogenic disorder of skeletal muscle calcium regulation, resulting from general anesthesia that can be fatal. Most cases are caused by administration of volatile anesthetics or depolarizing muscle relaxants.
It has been generally reported that both of sevoflurane and succinylcholine can induce the delayed onset of MH.
Here, we report a case of malignant hyperthermia in a four-year-old girl during anesthesia induction for unilateral congenital ptosis surgery, two minutes after sevoflurane and succinylcholine administration. The crisis was atypical but early recognized and managed by administration of dantrolene with symptomatic treatment.

Keywords: Malignant hyperthermia, Congenital ptosis, Sevoflurane, Succinylcholine

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Introduction

Malignant hyperthermia (MH) is a rare pharmacogenic myopathy that was described as a fatal complication of general anesthesia. The incidence of MH reactions ranges from 1:10,000 to 1: 250,000 anesthetics.[1] It's usually triggered by halogenated anesthetic agents with or without depolarizing muscle relaxants.[2]

MH is a state of an increased body metabolism, high fever and muscle rigidity. It's potentially life-threatening because of hyperkalemia, renal failure and multisystem organ failure.

The use of dantrolene and the avoidance of triggering agents in susceptible people have markedly reduced the mortality of this condition.[1]

In this case, we report congenital unilateral ptosis as the only ophthalmic finding in a four-year old girl who presented a MH during eyelid surgery. We highlight the importance of early recognition of this condition and the phenotype that allows suspecting it.

Case report

A four-year-old female child weighing 11 kg (−2.7 standard deviations) with congenital ptosis of the left eyelid was scheduled for surgical treatment under general anesthesia. On preanesthetic evaluation, the patient had no comorbid condition, was not on any drugs, and had no previous anesthetic exposure.

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[a] Department of Anesthesiology-Intensive Care, University Hospital Farhat Hached, Sousse, Tunisia
[b] Department of Medical Genetics, Faculty of Medicine of Sousse, Sousse, Tunisia
[c] Department of Pediatrics, University Hospital Farhat Hached, Sousse, Tunisia

* Corresponding author.
e-mail address: fehmiferhi@hotmail.fr (F. Ferhi).

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She was born at term following an uneventful pregnancy from non-consanguineous parents. Neither the patient nor her family had any history of neuromuscular disease or a special family history. The preoperative laboratory examinations were within the normal values, her creatine phosphokinase (CPK) level was 50 IU/L. She underwent general pediatric assessment. She had some subtle dysmorphic features including a high forehead, down-slanting palpebral fissures, epicanthic folds, a wide nasal bridge and low-set ears. Psycho-motor development was normal for age. There were no clinically detectable muscular weakness, and no neurological signs.

On ophthalmologic examination, there was a unilateral moderate ptosis of the left eyelid (Fig. 1). The patient had normal vision and normal ocular motility. There was no synkinesis detected. Pupils were normal. Anterior and posterior segment examinations were also normal.

In the operating theatre, airway equipment, anesthetic machine, adequate oxygen and personnel monitoring were checked.

Before induction of anesthesia, her blood pressure was at 115/75 mmHg, heart rate at 120 beats per minute (bpm), oxygen saturation (SaO_2) at 100%, body temperature at 36.7 °C and respiratory rate at 18 breaths/minute.

After preoxygenation, anesthesia was induced with sevoflurane 7% with fractional concentration of oxygen in inspired gas (FiO_2) at 1, an intravenous cannula was placed. She received 40 mg of propofol and 10 mg of succinylcholine.

Two minutes later we noticed tachycardia at 145 bpm and significant muscle contracture with stiffness especially in masseter muscle. The end-tidal pressure of carbon dioxide ($PETCO_2$) increased to 50 mmHg. The temperature and oxygen saturation were stable respectively at 36.8 °C and 100%.

Fig. 1. Patient at age 4. Unilateral moderate ptosis of the left eyelid. Subtle dysmorphic features: high forehead, down-slanting palpebral fissures, epicanthic folds, a wide nasal bridge and low-set ears.

MH was suspected, thus the use of sevoflurane was stopped. We deepened sedation with 80 mg of propofol and 2 μg of sufentanyl, the patient was intubated with a size 4.5 cuffed endotracheal tube which was inserted without any difficulty under direct laryngoscopy. Then she was hyperventilated with 100% of oxygen through a new ventilation circuit, consequently the $PETCO_2$ decreased to 30 mmHg. To maintain anesthesia propofol infusion and sufentanyl were started.

Her arterial blood gas was consistent with mixed acidosis: pH of 7.17, partial pressure of carbon dioxide in arterial blood (PaCO2) of 48 mmHg, partial pressure of oxygen in arterial blood (PaO2) of 366 mmHg, bicarbonate (HCO3-) of 16.7 mmol/L and base excess of −10. Her CPK level increased significantly from 50 to 10710 IU/L. Her urine was straw-colored with a red tinge.

Dantrolene sodium was administrated with the following protocol: 20 mg as a loading dose and maintaining dose of 20 mg during 2 h. We resort to hyperhydration, and sodium bicarbonate.

She immediately responded to the treatment. Her PETCO2 subsequently decreased to 36 mmHg, her pulse from 145 to 110 bpm; her temperature and blood pressure remained stable. The surgery was not performed.

According to the malignant hyperthermia clinical grading scale described by Larach et al.,[3] the raw score was 93 (Table 1), and the MH rank was 6 which indicates that MH was almost certain in our patient (Table 2).

The patient showed during 1 h and 40 min of anesthesia a stable temperature at 36.8 °C; a blood pressure at 115/67 mmHg and a heart rate ranging from 110 to 140 bpm.

Approximately 6 h after the onset of MH, we stopped sedation; the patient regained her normal level of consciousness. She was extubated and hospitalized in the pediatric intensive care unit for further observation. The arterial blood gas analysis showed a pH of 7.37, a $PaCO_2$ of 39.0 mmHg, a PaO_2 of 186 mmHg and $HCO3^-$ of 23.10 mmol/L.

One day later, the patient was out of the intensive care unit and was kept under clinical and biological surveillance especially for the rhabdomyolysis markers. No Further

Table 1. MH score in our patient.

Clinical indicators	Points
General muscular rigidity	15
Masseter spasm shortly following succinylcholine administration	15
Cola colored urine in perioperative period	10
Inappropriate hypercarbia	15
Inappropriate tachypnea	10
Inappropriate sinus tachycardia	3
Arterial base excess more negative than −8 mEq/L	10
Arterial ph < 7.25	10
Rapid reversal of MH signs of metabolic and/or respiratory acidosis with IV dantrolene	5
Total score	**93**

Table 2. Raw score, MH rank and their interpretation.[3]

Raw score	MH rank	Description of likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Somewhat less than likely
20–34	4	Somewhat greater than likely
35–49	5	Very likely
50+	6	Almost certain

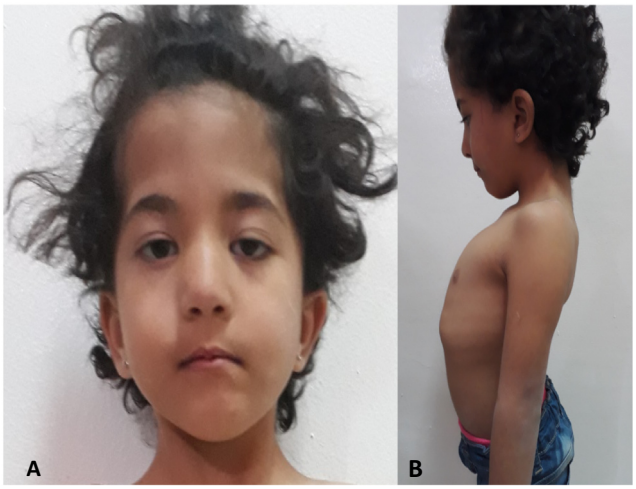

Fig. 2. Patient at age 8. (A): Dysmorphic features: high forehead, ptosis of the left eyelid, down-slanting palpebral fissures, hypertelorism, epicanthic folds, arched eyebrows, low-set ears. (B): Thoracic deformation and lumbar lordosis.

investigations were done. She was discharged from the hospital 4 days after the onset of MH without any problem. Parents opted against any further surgical procedure for her ptosis.

The patient was seen in follow up, four years later with more evident dysmorphic features, and skeletal abnormalities (Fig. 2). She had high forehead, ptosis of the left eyelid, down-slanting palpebral fissures, hypertelorism, epicanthic folds, arched eyebrows, low-set ears, pectus excavatum, thoracic deformation, lumbar lordosis and mild proximal weakness. The association of these clinical features with MH evoked the King-Denborough syndrome.

Discussion

MH is a rare and potentially lethal pharmacogenic disorder of skeletal muscle regulation.[4,5] Most cases are triggered by administration of volatile anesthetics or depolarizing muscle relaxants such as succinylcholine.[6] The use of these substances causes the release of calcium stores from the sarcoplasmic reticulum and the entry of calcium from the myoplasm. This leads to a hypermetabolic cascade involving contracture of skeletal muscles, glycogenolysis, depletion of adenosine triphosphate and muscle cell death, responsible for hyperthermia and excess lactate.[4,7–9]

The estimated incidence of MH ranges from 1:10,000 to 1:250,000 anesthetics. MH episodes are becoming rarer with the increasing use of non-triggering intravenous anesthetics and the avoidance of succinylcholine.[10] The estimated prevalence of genetic abnormalities associated with MH susceptibility ranges from 1:3000 to 1:8500. Recently, it is estimated to be 1:400 after analyzing exome data and identification of several mutations leading to MH susceptibility which is usually inherited as an autosomal dominant trait.[1,10,11] The estimated overall sex ratio is of 3 males per 1 female.[12,13] All ethnic groups are affected, in all parts of the world. The highest incidence is in young people, with a mean age of all reactions of 18.3 years. It has been found that children under 15 years age comprised 52.1% of all reactions.[14,15]

Larach et al. gave a clinical grading scale using clinical indicators for determining the MH raw Score.[3,15] The parameters used were rigidity, muscle breakdown, respiratory acidosis, hyperthermia, cardiac involvement, family history of MH and some biochemical parameters. These parameters were given points according to the MH rank and these were added up to get the MH raw score. The total score in our patient was 93 which put her in MH rank 6 making the diagnosis of malignant hyperthermia almost certain.

Usually, the first signs of MH are tachycardia and an increase in $PETCO_2$. Hyperthermia is considered as late sign.[16] As compared with the other case reports, our patient's $PETCO_2$ had increased within 2 minutes after anesthetic induction with sevoflurane and succinylcholine. The occurrence of MH was strongly considered because of the tachycardia and masseter rigidity, although body temperature hadn't increase yet.

Early recognition and treatment are essential in reducing MH-associated morbidity and mortality.[17] In fact, mortality without specific prompt treatment is of 80% and drops to <5% with the use of dantrolene sodium.[1] Treatment with dantrolene is usually initiated when MH is strongly suspected; it binds to the ryanodine receptors and blocks calcium release, thereby halting the uncontrolled muscle contractions.

MH is inherited as an autosomal dominant trait with reduced penetrance. The majority of reported cases are caused by mutations in two genes: *RYR1* gene (ryanodine receptor type 1) and *CACNA1S* gene (voltage-dependent L type calcium channel alpha 1S subunit) which are estimated to account for approximately 70% and 1% of MH susceptibility, respectively. These two genes are related to skeletal muscle calcium regulation.[5] Recently, mutations in *STAC3* have been identified in five families with Native American Myopathy, associated with increased MH susceptibility.[5,18]

Dominant or recessive mutations in *RYR1* are the most commonly identified cause of inherited neuromuscular disease and also of malignant hyperthermia susceptibility.[4,19,20]

The ryanodine receptor is located in the sarcoplasmic reticulum membrane of skeletal muscle cells and is important for excitation-contraction coupling and maintenance of Ca^{2+} homeostasis.[5,21]

The abnormal receptor releases excess calcium once triggered by specific agents, mainly succinylcholine and/or the halogenated inhalation agents.[22]

The *RYR1* gene (OMIM 180901) on chromosome 19q13.1 is a 106-exon gene with more than 150,000 base pairs, which makes its sequencing really difficult.[23] It is known to be a polymorphic gene with more than 170 missense mutations, most of them considered as polymorphisms rather than causative mutations.[24]

The number of known mutations is rapidly increasing with the use of next generation sequencing.[5,11] Currently, there are 48 *RYR1* mutations proven to be causative for MH.[7,25]

RYR1 mutations have been associated with a broad spectrum of clinical phenotypes. The most common of the RYR1-myopathies are central core disease (typically dominant) and multiminicore disease (typically recessive).[4,19]

Ptosis was described by Albakri et al. in *RYR1*-related myopathy. They report congenital ptosis as the only ophthalmic findings in 2 siblings with scoliosis and underlying recessive *RYR1* mutations.[4] D'Arcy CE reported pathogenic

variants in *RYR1* that have been found in some individuals with King or King-Denborough syndrome which associates ptosis, down-slanting palpebral fissures, hypertelorism, epicanthic folds, low-set ears, malar hypoplasia, micrognathia, high-arched palate, clinodactyly, palmar simian line, pectus excavatum, winging of the scapulae, lumbar lordosis and mild thoracic scoliosis who present congenital hypotonia, slightly delayed motor development, diffuse joint hyperextensibility and mild proximal weakness. King-Denborough syndrome is known to predispose to MH. Although the cause of King-Denborough syndrome is not fully understood, some cases have been attributed to *RYR1* gene.[26,27]

Several features of King-Denborough syndrome were present in our patient which makes this diagnostic the most plausible.

In clinical anesthesia practice, MH susceptibility has often been assumed in patients with nonspecific muscle weakness but without a definitive diagnosis.[7] This shotgun approach can represent the best choice when no genetic or neuromuscular pre-surgical explorations are performed. In this study, although the patient presented an apparently isolated congenital ptosis without ophthalmoplegia, or any other muscular findings, she developed a MH crisis during general anesthesia.

This highlights the importance of MH's risk suspicion when such phenotype is present, which would reflect an underlying *RYR1* mutation.

There is no specific expression of MH but only in front of a typical crisis that we can suspect it. That's why; it would be great if a systematic presymptomatic molecular diagnosis is available.

Genetic testing of *RYR1*, when possible, is indicated for all patients with MH, and anesthetic precautions should be considered for any child with symptoms of neuromuscular disease.[5] Unfortunately, because of a high allelic and locus heterogeneity in MH, absence of *RYR1* mutations does not exclude MH diagnosis. In fact, sensitivity of genetic testing is estimated to be approximately 25%.[28]

Hence, a negative molecular genetic test should be followed by contracture testing, as open muscle biopsy with contracture testing is the only possible means to exclude MH, when negative.[17,29,30]

In this study, molecular genetic testing couldn't be performed. In fact, with 106 exons, *RYR1* is expensive and time consuming to Sanger sequence for clinical diagnostics.[31] Exome sequencing which is the most efficient tool to identify recurrent or novel *RYR1* mutations, was not available. MH was early suspected and managed in this patient because of the presence of congenital ptosis.

When MH susceptibility is suspected, prolonged general anesthesia, potent triggering inhalation anesthetics and depolarizing muscle relaxants should be avoided. Anesthesiologists should opt rather for Non-triggering anesthetics (such as opioids, barbiturates, propofol, benzodiazepines, ketamine, *etc.*) and monitored anesthetic care with adequate postoperative monitoring.[4,32,33]

In the case studied, muscle rigidity and an increase in $PETCO_2$ alarmed us to suspect MH especially that sevoflurane and succinylcholine were used. Stopping sevoflurane and starting immediately administration dantrolene saved the patient.

MH should be early recognized and managed by dantrolene that should be provided in every operating theatre.

Patients with congenital ptosis should be considered MH susceptible not only when other clinical features evoking a myopathy are present, but also when there are some subtle dysmorphic features that may be related to MH susceptibility syndromes such as King-Denborough syndrome.

Conflict of interest

The authors declared that there is no conflict of interest.

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