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Key Words

Malignant Hyperthermia (MH); Ryanodine Receptor; Central Core Disease (CCD); Core Myopathies

Abbreviations

MH: Malignant Hyperthermia; CCD: Central Core Disease; RYR1: Ryanodine Receptor; IVCT: *In Vitro* Contracture Testing; PICU: Pediatric Intensive care Unit

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Case Report

Malignant Hyperthermia and Absence of Ryanodine Receptors in a Child Presenting for Ptosis Repair

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Abstract

Introduction: Malignant hyperthermia (MH) is a hypermetabolic condition caused by a genetic cell membranes channel disruption leading to increased calcium release from the sarcoplasmic reticulum after exposure to triggering agents. Central Core Disease (CCD) is a rare inherited neuromuscular disorder with a wide spectrum of phenotypic presentations. Clinically, there is muscle weakness of variable degree and histopathologically there is evidence of core formation in the muscle fibers. Additional features may occur, including skeletal abnormalities such as foot deformities, scoliosis, or hip displacement. Association of CCD with a mutation of the ryanodine receptor RYR1 and MH is high. If not properly treated, MH could be fatal.

Purpose: This study aims towards increasing the awareness of pediatricians, surgeons and anesthesiologists about possible occurrence of MH in patients presenting with only mild “clinical” signs of congenital myopathies such as CCD. Careful diagnostic investigations should be performed prior to surgical interventions and extreme caution during anesthesia.

Material and Methods: We report the case of a 3 years old girl, with a history of ptosis, scoliosis, and good muscle tone, who developed unexpected MH during the surgical repair of her ptosis. The critically ill child was transferred to Pediatric Intensive Care Unit (PICU) for management of her MH. The management was done following the guidelines of the European Malignant Hyperthermia Group published in the British Journal of Anesthesia 2010. The patient responded well to treatment. She had a muscle biopsy done after recovery.

Discussion: Early management and dantrolene administration are the most important factors to minimize MH morbidity and mortality. MH susceptibility is known in patients carrying mutations in the RYR1 receptors. In our case, RYR1 staining was negative on the muscle biopsy specimen suggesting abnormal or absent RYR1 function, with the presence of occasional cores. These findings, in addition to the ophthalmological and orthopedic history were diagnostic of CCD. *In Vitro* Contracture Testing (IVCT) was not done because it was not available. Genetic testing was refused by the parents due to financial reasons.

Conclusion: In patients presenting with symptoms suggestive of muscle weakness, such as ptosis and scoliosis, and variable muscle tone; congenital myopathies should be considered. CCD and RYR1 receptors deficiency or mutation, if present, may lead to a possible risk of fatal MH, which can be prevented.

Introduction

Malignant Hyperthermia (MH) is a potentially fatal pharmacogenetic disease of the skeletal muscle triggered by exposure to commonly used potent inhalation anesthetics and/or the depolarizing muscle relaxant Succinylcholine. It is rarely triggered by stress or vigorous exercise or heat [1-3]. The MH crisis results from the uncontrolled release of Calcium (Ca^{2+}) into the skeletal muscle cytoplasm, which induces a hypermetabolic state characterized by excessive heat production, acidosis and rhabdomyolysis. In almost all cases of MH, the calcium is excessively released into the cytoplasm due to a defective calcium channel located in the sarcoplasmic reticulum membrane, termed the Ryanodine Receptor (RYR1) [1-5]. Central Core Disease (CCD) is a rare inherited congenital myopathy characterized by central cores with absence of oxidative and glycolytic enzymatic activity on muscle biopsy [6]. The disease is dominantly inherited, rarely recessive, and may present in infancy with hypotonia, delayed motor milestones and proximal muscle weakness. It may also present with isolated orthopedic and ophthalmological complications such as scoliosis, congenital hip dislocation or ptosis [6-8]. Patients with core myopathies, particularly CCD, are highly susceptible to MH due to the mutation of the skeletal RYR1 gene at chromosome 19 [6,7,9-13]. We therefore report in this article, the rare case of a three years old girl with features of congenital myopathy, not previously investigated, who developed MH during surgical correction of her ptosis.

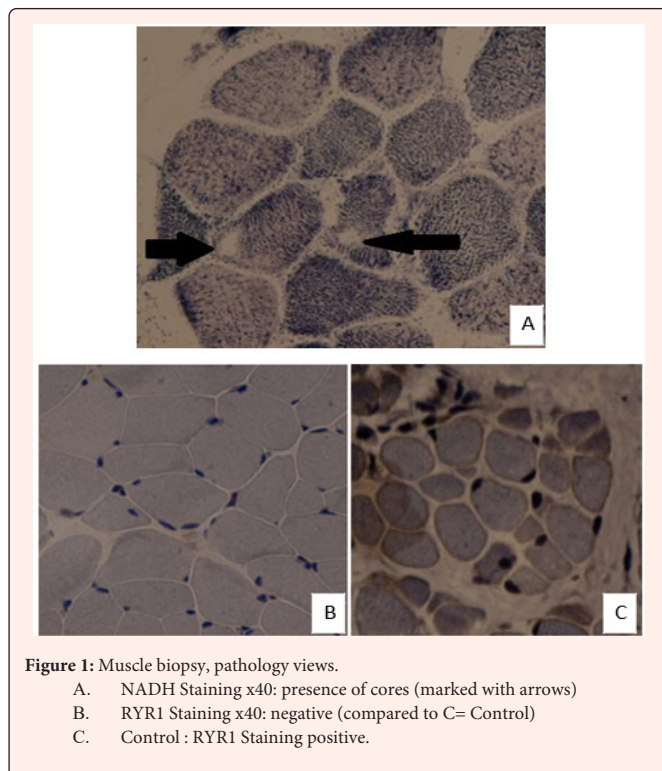
Case Report

A 3 years old girl known to have failure to thrive, scoliosis and bilateral congenital ptosis, not investigated before, presented for ophthalmological repair of her ptosis. The girl was otherwise healthy, had no familial history of anesthesia-related events or myopathies. Before surgery, she received induction anesthesia with Sevoflurane and Nitrous Oxide, followed by endotracheal intubation. Five minutes later, she developed tachycardia reaching 200bpm with progressive increase in the $EtCO_2$ (~100mmHg), trismus and generalized rigidity. Her temperature rose from 37°C to reach 39.9°C within 15 minutes from induction. Malignant hyperthermia was strongly suspected, so the inhaled anesthetics were immediately discontinued and the surgeon was asked to stop the surgery. The management was done following the guidelines of the European Malignant Hyperthermia Group published in the British Journal of Anesthesia 2010 [14]. Hyperventilation with 100% oxygen and cooling was applied on IV

sites. She was transferred to the Pediatric Intensive Care Unit (PICU) for monitoring and management. Hydration was set to 2000mL/24hrs. Dantrolene IV was started to a cumulative dosing not exceeding 10mg/Kg/day. Bicarbonate was given for acidosis on Arterial Blood Gases (pH=7.16). Furosemide and mannitol were also administered to stimulate diuresis. Her initial laboratory tests showed a high serum Creatine Kinase (CK) level of 3953IU and normal CBC, electrolytes, BUN, creatinine and liver transaminases. Myoglobin in urine was negative, and this was maybe due to the early management. She transiently developed hyperthermia exceeding 38.5°C treated by cooling and dantrolene. Acidosis progressively normalized on arterial blood gases, but serum CK levels continued to rise to reach 6383IU, on day 5 after surgery, and then decreased progressively to normal values. Complete defervescence was achieved after 48 hours. The patient was successfully extubated on day 8 post-surgery. Muscle biopsy was done after recovery that showed evidence of rhabdomyolysis, core formations and absence of RYR1 staining (Figure 1). *In Vitro* Contracture Testing (IVCT) was not done due to unavailability. Genetic testing was refused by the parents due to financial reasons.

a cost-effective method to diagnose MH susceptibility in the developed countries but it lacks sensitivity. Only 50% of MH susceptible patients carry a known genetic mutation [11,17]. Unfortunately, in Lebanon, genetic testing is very costly and was refused by the parents of the child due to financial reasons.

The muscle biopsy with IVCT is done as a first-line test in patients who are considered to be highly susceptible to MH or when genetic testing has not confirmed the MH susceptibility [16,17]. The IVCT test is not available in most of the laboratories in Lebanon and therefore, it was not done in our patient. Otherwise, the muscle biopsy showed features of a primary myopathy including occasional early core formation. There was also lipid accumulation and few degenerating fibers that are consistent with myofiber regeneration following episodes of induced rhabdomyolysis. Immunohistochemical staining of RYR1 receptors was negative and in favor of a genetic deficiency of those receptors. That deficiency was most probably responsible for the MH susceptibility (Figure1). Congenital myopathies with cores, and more specifically CCD, carry a high risk of MH susceptibility due to RYR1 mutations [6,7,9,10,12,13]. CCD is a rare myopathy that is inherited dominantly and is diagnosed based on clinical and histopathological findings on muscle biopsy. MH could be the diagnosing factor [6]. The clinical presentation is marked by a variable degree of muscle weakness, from severe hypotonia in infancy and delayed milestones, to a mild involvement of the facial musculature and the eyelids (ptosis). It is also highly associated with orthopedic abnormalities such as congenital hip dislocation, scoliosis and foot deformities. The diagnosis is confirmed based on histopathological findings on muscle biopsy marked by the presence of cores that lack oxidative and glycolytic activities [6-8]. Our patient's history, clinical features, MH susceptibility and muscle biopsy findings were all diagnostic of CCD.



Conclusion

Congenital myopathies like CCD may present with “benign” and non specific clinical signs and symptoms. Those findings should raise the awareness of anesthesiologists, orthopaedic surgeons and ophthalmologists about the possibility of a congenital myopathy like CCD. CCD and related myopathies are highly associated with RYR1 mutations that increase MH susceptibility. Precautions should be taken pre and peri-operatively to avoid any trigger medications and dantrolene should be readily available in case of a MH crisis.

References

- Rosenberg H, Davis M, James D, Pollock N, Stowell K (2007) Malignant Hyperthermia. *Orphanet J Rare Dis* 2: 21.
- Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K (2015) Malignant hyperthermia: A review. *Orphanet J Rare Dis* 10: 93.
- Kaur H, Katyal N, Yelam A, Kumar K, Srivastava H, et al. (2019) Malignant hyperthermia. *Mo Med* 116(2): 154-159.
- Kaufmann A, Kraft B, Michalek-Sauberer A, Weigl LG (2008) Novel ryanodine receptor mutation that may cause malignant hyperthermia. *Anesthesiology* 109(3): 457-464.
- Carpenter D, Hopkins PM, Robinson RL, Quinnell RJ, Ringrose C, et al. (2009) Genetic variation in RYR₁ and malignant hyperthermia phenotypes. *Br J Anaesth* 103(4): 538-548.
- Jungbluth H (2007) Central core disease. *Orphanet J of Rare Dis* 2: 25.
- Quinlivan RM, Sewry CA, Muller CR, Davis M, Laing NG, et al. (2003) Central core disease: Clinical, pathological, and genetic features. *Arch Dis Child* 88(12): 1051-1055.
- Gamble JG, Rinsky LA, Lee JH (1988) Orthopaedic aspects of central core disease. *J Bone Joint Surg Am* 70(7): 1061-1066.
- Klingler W, Rueffert H, Lehmann-Horn F, Girard T, Hopkins PM (2009) Core myopathies and risk of malignant hyperthermia. *Anesth Analg* 109(4): 1167-1173.
- Treves S, Jungbluth H, Muntoni F, Zorzato F (2008) Congenital muscle disorders with cores: The ryanodine receptor calcium channel paradigm. *Curr Opin Pharmacol* 8(3): 319-326.
- Riaz S, Kraeva N, Hopkins PM (2018) Malignant hyperthermia in the post-genomics era: New perspectives on an old concept. *Anesthesiology* 128(1): 168-180.
- Brislin RP, Theroux MC (2013) Core myopathies and malignant hyperthermia susceptibility: A review. *Paediatr Anaesth* 23(9): 834-841.

Discussion

MH crisis is a potentially fatal disease if not properly treated. Dantrolene in addition to early diagnosis and management are the major game changers [2,15] which have caused a decline of the mortality rate from 80% to less than 5% in the last 30 years [1,2]. Luckily, our patient was diagnosed and managed rapidly. Dantrolene was also readily available in the PICU, which helped in reversing the MH crisis and limit the morbidity. The management was done following the European Malignant Hyperthermia Group guidelines published in the British Journal of Anesthesia 2010 [14]. It consisted of immediate actions that were initiated in the operating room: stopping the triggering anesthetic agent, hyperventilating with 100% oxygen and cooling at IV sites. Dantrolene IV infusion was started upon arrival to the PICU. Additional treatment was given to treat acidosis with sodium bicarbonate and to stimulate diuresis with furosemide and mannitol. There were no hyperkalemia, myoglobinuria or cardiac arrhythmias noted. The rise of the serum CK levels was indicative of a rhabdomyolysis but it was reversed by the early and efficient management. New guidelines advise adding activated charcoal filters on inspiratory and expiratory circuits during early management [15]. They also advise genetic testing and/or muscle biopsy with IVCT to prove MH susceptibility [15,16]. Genetic testing for a mutation in the known genes responsible for MH such as RYR1, is



13. Robinson R, Carpenter D, Shaw MA, Halsall J, Hopkins P (2006) Mutations in RYR1 in malignant hyperthermia and central core disease. *Hum Mutat* 27(10): 977-989.
14. Glahn KPE, Ellis FR, Halsall PJ, Muller CR, Snoeck MMJ, et al. (2010) Recognizing and managing a malignant hyperthermia crisis: Guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth* 105(4): 417-420.
15. Hopkins PM, Girard T, Dalay S, Jenkins B, Thacker A, et al. (2021) Malignant hyperthermia 2020: Guideline from the association of Anaesthetists. *Anaesthesia* 76(5): 655-664.
16. Hopkins PM, Rüffert H, Snoeck MM, Girard T, Glahn KPE, et al. (2015) European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *Br J Anaesth* 115(4): 531-539.
17. Rosenberg H, Sambuughin N, Riazi S, Dirksen R, Adam MP (2003) Malignant hyperthermia susceptibility. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, (eds.), *Gene Reviews*, University of Washington, USA, pp. 1993-2022.