Can J Anesth/J Can Anesth (2023) 70:169–171
https://doi.org/10.1007/s12630-022-02355-5

CORRESPONDENCE

Awake malignant hyperthermia: report of a case to help prevent crises in operating rooms

Natalia Puerto, MD · Kazuyoshi Aoyama, MD, PhD · Tara Der, MD · Igor Luginbuehl, MD · Cengiz Karsli, MD · Reinhard Zeller, MD · Christian Zaarour, MD

Received: 30 August 2022 / Revised: 6 October 2022 / Accepted: 6 October 2022 / Published online: 11 November 2022

Keywords creatine kinase · dantrolene · malignant hyperthermia · mutation · pediatrics · ryanodine receptor

To the Editor,

Rare malignant hyperthermia (MH) crises termed "nonanesthetic," "awake MH," or "MH-like" reactions may present outside the operating room or without anesthetic triggers,[1–3] incited by viral infections, stress, and dehydration.[1–3] Dantrolene is used to prevent and treat these cases. Awake MH presents as a hypermetabolic state (e.g., hyperthermia, sustained contracture, rhabdomyolysis, hyperkalemia); unrecognized and untreated, it can progress to arrhythmias and cardiac arrest. Diagnosing, preventing, and treating awake MH remain challenging. We report on the perioperative management of a pediatric patient with a history of awake MH episodes. Written informed consent was obtained from the patient's legal guardian for the publication of this report.

A 12-yr-old, 29-kg girl with severe scoliosis due to a congenital myopathy secondary to compound heterozygous Ryanodine receptor type 1 (RYR1) variants (Figure, panels A and B) presented for spinal fusion and instrumentation. Her first MH episode was at ten months during a muscle biopsy, triggered by sevoflurane, resulting in rigidity, hyperthermia, hyperlactatemia, acidosis and elevated creatine kinase (CK), requiring two doses of intravenous dantrolene and a 48-hr stay in the intensive care unit (ICU). Tests revealed a central nuclear myopathy related to a heterozygous RYR1 receptor mutation (Figure, panel B). At five years, she experienced nonanesthetic awake MH crises: one resolved spontaneously and two were life-threatening,[3] occurring in the context of viral infection and/or minor trauma. She developed ventricular tachycardia after a period of progressive fatigue, fever, and rigidity, and CK levels spiked to 20,000 $U \cdot L^{-1}$. She required repeated doses of dantrolene. A few years later, dental restorations led to another dantrolene-treated MH crisis, despite trigger-free anesthesia. She was not compliant with a preventative oral dantrolene prescription (0.5 $mg \cdot kg^{-1}$ twice a day)[4] but experienced no awake MH crisis until her spinal surgery.

The patient's thoracolumbar curvature increased (31 to 97 degrees) due to her RYR1 myopathy (Figure, panel A) and surgical correction was chosen. Preoperatively, she received

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-022-02355-5.

N. Puerto, MD
Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada

Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada

K. Aoyama, MD, PhD (✉)
Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada
e-mail: kazu.aoyama@utoronto.ca

Program in Child Health Evaluative Sciences, SickKids Research Institute, Toronto, ON, Canada

T. Der, MD · I. Luginbuehl, MD · C. Karsli, MD · C. Zaarour, MD
Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada

R. Zeller, MD
Division of Orthopaedic Surgery-Head and Spine Program, The Hospital for Sick Children, Toronto, ON, Canada

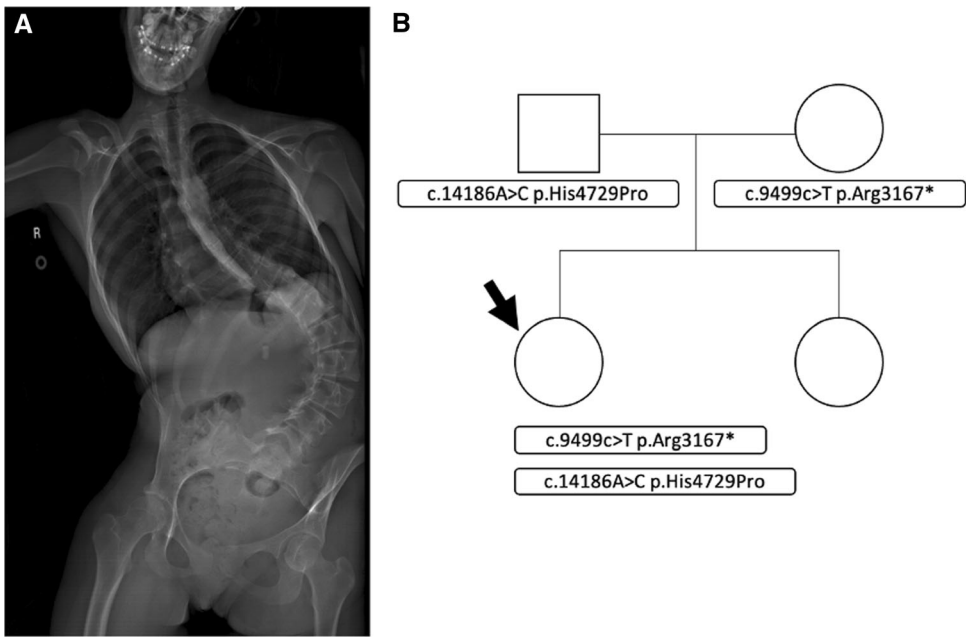

Figure A) Severe scoliosis with thoracolumbar curvature of 68 degrees. B) Pedigree showing heterozygous mutation in two exons of the RYR1 gene. The first one is exon 64 of the RYR1 gene for a variant defined as c.9499C>T (inherited maternally), which is predicted to result in premature protein termination (p.Arg3167*). This variant is expected to be causative for recessive, congenital RYR1 myopathy. The second one is exon 98 of the RYR1 gene for an undocumented variant of uncertain clinical significance defined as c.14186A>C (inherited paternally), which is predicted to result in an amino acid substitution (p.His4729Pro). The p.His4729Pro residue is moderately conserved among RYR1 proteins. Substitutions of nearby amino acids such as p.Tyr4733Asp and p.Gly4634Glu are reported to be pathogenic.[5] There was no history of MH or congenital myopathy in the family. MH = malignant hyperthermia; RYR1 = Ryanodine receptor type 1

oral lorazepam for anxiety and dantrolene 2.5 $mg \cdot kg^{-1}$ *iv* over one hour, then an infusion of 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ until at least post surgery. Anesthetic induction with fentanyl, propofol, and rocuronium was followed by tracheal intubation. Propofol, remifentanil, and tranexamic acid maintained trigger-free anesthesia and reduced bleeding. After intubation, the CK level spiked to 2,781 $U \cdot L^{-1}$ (baseline: 753 $U \cdot L^{-1}$) without a MH crisis and then declined. The spinal surgery lasted nearly seven hours, postoperative ICU care included dantrolene (0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ *iv*) and ventilatory support. After nine hours without CK levels increasing, dantrolene was discontinued, extubation occurred, and the CK level increased to 3,793 $U \cdot L^{-1}$ then returned to baseline without metabolic disturbances. Her postoperative course was uneventful.

Awake and classic MH share pathophysiologic mechanisms but not genetics. While our patient carried two mutations on different alleles (Figure, panel B),[3] single RYR1 mutations have been found in other awake MH patients.[1,2] Awake MH patients can develop severe and fatal reactions to emotional or physical triggers (e.g., pain, stress).[1–3]

Current evidence is unclear if prophylactic dantrolene decreases MH risk in patients with a history of awake MH. While how early, what dose, and how long dantrolene should be administered remain unclear, those with susceptibility to classic MH have benefited from oral prophylactic dantrolene to prevent and reduce the severity and frequency of symptoms related to RYR1 mutations.[2,4] Our MEDLINE literature search of awake MH on 3 November 2021 (Electronic Supplementary Material, eAppendix) resulted in 242 papers, but no cases of pediatric awake MH receiving preoperative dantrolene to prevent a crisis were reported. This indicates that more research is needed.

Although guidelines outline adequate perioperative preparation for patients at risk of an MH crisis, the use of prophylactic dantrolene in awake MH patients seems inconclusive. Anesthesiologists need to consider the risk of each case separately and continually re-evaluate the patients for signs of MH to establish early prophylaxis or treatment.

Acknowledgements Kazuyoshi Aoyama acknowledges the Department of Anesthesiology and Pain Medicine, University of Toronto, and the Hospital for Sick Children, for secured academic time to conduct the current work as a recipient of Merit Awards.

Disclosures The authors declare that there is no conflict of interest.

Funding statement This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Editorial responsibility This submission was handled by Dr. Stephan K. W. Schwarz, Editor-in-Chief, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.*

References

1. *Zvaritch E, Gillies R, Kraeva N, Richer M, Jungbluth H, Riazi S*. Fatal awake malignant hyperthermia episodes in a family with malignant hyperthermia susceptibility: a case series. Can J Anesth 2019; 66: 540–5. https://doi.org/10.1007/s12630-019-01320-z
2. *Groom L, Muldoon SM, Tang ZZ, et al*. Identical de novo mutation in the type 1 ryanodine receptor gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. Anesthesiology 2011; 115: 938–45. https://doi.org/10.1097/aln.0b013e3182320068
3. *Cummings T, Der T, Karsli C*. Repeated nonanesthetic malignant hyperthermia reactions in a child. Pediatr Anesth 2016; 26: 1202–3. https://doi.org/10.1111/pan.13006
4. *Timmins MA, Rosenberg H, Larach MG, Sterling C, Kraeva N, Riazi S*. Malignant hyperthermia testing in probands without adverse anesthetic reaction. Anesthesiology 2015; 123: 548–56. https://doi.org/10.1097/ALN.0000000000000732
5. *Robinson R, Carpenter D, Shaw MA, Halsall J, Hopkins P*. Mutations in RYR1 in malignant hyperthermia and central core disease. Hum Mutat 2006; 27: 977–89. https://doi.org/10.1002/humu.20356