2011

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Biochimica et Biophysica Acta xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Commentary

Malignant hyperthermia — Human stress triggering

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ARTICLE INFO

Article history:
Received 6 May 2011
Received in revised form 20 July 2011
Accepted 20 July 2011
Available online xxxx

Keywords:
malignant hyperthermia
muscle rigidity
hypercarbia
genetic analysis

ABSTRACT

Letter to the Editor concerns the question of a discussion of awake porcine malignant hyperthermia that erroneously omits the awake human stress reaction of malignant hyperthermia.

Letter to the Editor regarding the article:

D.H. Maclennan, E. Zvaritch, Mechanistic models for muscle diseases and disorders originating in the sarcoplasmic reticulum, Biochim. Biophys. Acta 1813 (2011) 948-964.

Drs. MacLennan and Zvaritch have a commendable presentation on muscle disorders related to sarcoplasmic reticulum. However, we call attention to their statement, page 950, left column, lines 6–9, that, while swine can trigger into a malignant hyperthermia (MH) reaction under stressful conditions, humans do not. Specifically, they state,

"… triggering of an MH reaction, … requires the presence of both a causal mutation and either a triggering anesthetic, or, in the case of pigs, stressful conditions."

Yet there is indisputable evidence that humans susceptible to MH have stress-related abnormal responses in the absence of exposure to triggering anesthetic agents:

Patient 1: In the late 1970s, this 42 y/o 5′ 10″ (175 cm) 200 lb (90 kg) white male came to the Mayo Clinic in Rochester for evaluation of periodic stressful overheating [1]. Evaluation by the internist Dr. Thompson reminded him of a presentation on MH provided by Dr. Gronert at an Internal Medicine seminar, and he requested my evaluation.

For the past 20–25 years extreme physical or emotional stress or fatigue had resulted in aching joints, malaise, fevers of 40 °C (104 °F) or more, and soaking sweats. These persisted despite use of aspirin and surface cooling. This 'fever' would break after 3–4 days. Prior medical workups documented these. Laboratory abnormalities occurred only during episodes and included mild hyperglycemia and a

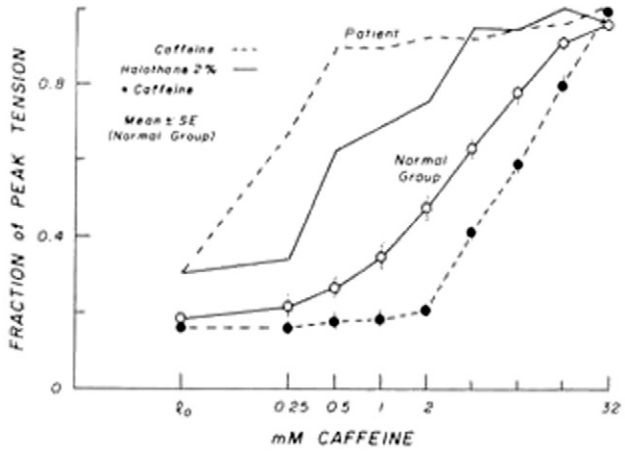

Fig. 1. Contracture dose–response curves of the patient's muscle compared to mean dose–response curves from a normal population. Note the shift to the left, indicating a lower threshold to caffeine in the presence or absence of halothane, l_o. Optimal length.

DOI of original article: 10.1016/j.bbamcr.2010.11.009.
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0167-4889/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2011.08.001

diabetic glucose tolerance test. He learned to avoid stresses that resulted in these episodes.

An extensive Mayo workup was normal except for skeletal muscle contracture responses to determine susceptibility to MH. At this time, national standardized contracture testing did not exist, and we compared his responses to normal values we had determined in normal humans [2].

His values differed from normal (Fig. 1 from [1]), consistent with susceptibility to MH:

We advised use of oral dantrolene when these symptoms recurred at home. It was wonderfully effective and "turned his life around." He could now be active physically without worry. The effective dose was 1.1 mg/kg; it relieved the symptoms within 2–3 h, also producing a mild weakness.

We have communicated over the years; in fall 2010 he related that he continues dantrolene control as needed, same dose. Several years after we diagnosed him as MH susceptible, he had added surgery at Mayo; he did fine with non-triggering agents, but, upon emergence and awakening, his symptoms began to recur, and were effectively treated with intravenous dantrolene.

The patient was enrolled in a study of MH genetics through the North American MH registry. Screening of 64 exons in the RYR1 gene did not identify a variant but screening of gene coding for myoadenylate deaminase (AMPD1 gene) revealed two mutations Q12X and P48L which are associated with AMPD1 deficiency, the most common enzyme defect in humans [3].

Patient 2: A 12 y/o boy developed MH during sevoflurane anesthesia for treatment of a humerus fracture [4]. Fifteen minutes after induction, end expired CO2 abruptly increased to more than 70 mm Hg, pulse rate to 150, temperature from 36.7° to 39.4 °C. Diaphoresis became evident. Treatment included dantrolene. CK, later, was 9049 International Units (IU). He recovered uneventfully.

Eight months later, he played football when the outside temperature was 80 °F (26 °C). After the game, he felt hot, was diaphoretic, and hyperventilated. He described tingling in his limbs. He convulsed, and had a respiratory arrest. His ECG showed a sinus tachycardia of 136. Jaw trismus prevented tracheal intubation. He developed ventricular fibrillation. Treatment included epinephrine and defibrillation. At the hospital, his rectal temperature was >108 °F (42.2 °C). He had a wide complex bradycardia, and, again, ventricular fibrillation. His trachea was intubated without relaxant. Treatment included bicarbonate, calcium, glucose, insulin, and dantrolene. Arterial sample: pH 6.76, PCO2 115, PO2 22, K + 8.8 mEq/l, increasing to 14.5 mEq/L. Resuscitation was halted after an hour. He had full rigor post mortem, and muscle histology was not grossly abnormal. Both the boy and his father had a mutation, R163C, in the RYR1 gene.

Patient 3: A 7 month old male was given nitrous oxide/oxygen/halothane (0.5–1%) as anesthesia for bilateral ptosis repair [5]. He became dusky and rigid. Halothane was discontinued, 100% oxygen was started, and surgery was canceled. Rectal temperature peaked at 100 °F. CK 8 h later was 1883 IU.

At 20 months of age he had his first non-anesthetic MH-like event; this seemed to be related to a high environmental temperature. Over the next four years he had multiple episodes of muscle stiffness with fever, tachycardia, CK values to 100,000 IU, and hyperkalemia, associated with upper respiratory infections, or, even, spontaneously. Treatment consisted of cooling, analgesics, and dantrolene. At age 5, muscle biopsy data showed a contracture of 10 g to 3% halothane and 1.2 g with 2 mM caffeine, diagnostic of susceptibility to MH. During one of his febrile episodes, he died while en route to a hospital.

Patient 4: A 6 y/o girl was hospitalized with fever 102.7 °F (39.3 °C), rigidity, trismus, and emesis [5]. (In the past, she'd had a spontaneous episode of fever >105 °F (40.6 °C) plus total body and jaw muscle rigidity.) Despite therapy, she deteriorated, with temperature 108 °F (42.2°). Asystole occurred, cardiopulmonary resuscitation began, and intravenous dantrolene 10 mg/kg was given. She died despite 2 h cardiopulmonary resuscitation. Autopsy was unremarkable.

In both patients 3 and 4, genetic testing showed a novel amino acid change, Arg to Cys, at position 3983 (exon 87) of the RYR1 gene [5]. Arg at position 3983 is highly conserved among ryanodine subtypes and across species. This change was absent in all of 280 control chromosomes.

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Please cite this article as: G.A. Gronert, et al., Malignant hyperthermia — Human stress triggering, Biochim. Biophys. Acta (2011), doi:10.1016/j.bbamcr.2011.08.001