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Exertional Heat Stroke and Susceptibility to Malignant Hyperthermia in an Athlete: Evidence for a Link?

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Objective: To describe the possible association (pathophysiologic and clinical features) between exertional heat stroke (EHS) and malignant hyperthermia (MH).

Background: Both EHS and MH are acute and life-threatening disorders. It has repeatedly been shown that EHS can occur in well-trained patients with known MH-associated mutation in the *RYR1* gene in the absence of any extreme environmental conditions or extreme physical activity, thereby supporting a possible link between EHS and MH. In this case, a highly trained 30-year-old male athlete suddenly collapsed while running. He had initial hyperthermia (40.2°C) and progressive multiple organ failure requiring medical management in an intensive care unit. After he recovered completely, a maximal exercise test was performed and showed an obvious abnormality of oxidative metabolism in muscle; genetic analysis of the *RYR1* gene identified a heterozygous missense variation p.K1393R. Consequently, the athlete was given appropriate information and allowed to progressively return to sport competition.

Differential Diagnosis: Doping, use of drugs and toxic agents, exercise-associated hyponatremia, exertional heat illness.

Treatment: Initial management started with the basic resuscitative guidelines of airway, breathing, and circulation (intubation). Cooling, administration of fresh frozen plasma, and intensive rehydration resulted in improvement.

Uniqueness: To our knowledge, ours is the first description of this MH mutation (p.K1393R) in the *RYR1* gene that was associated with exertional rhabdomyolysis involving a dramatic impairment of oxidative metabolism in muscle.

Conclusions: Common features are shared by EHS and MH. Careful attention must therefore be paid to athletes who experience EHS, especially in temperate climates or when there are no other predisposing factors.

Key Words: *RYR1* gene, thermoregulation, heat illness, exertional rhabdomyolysis

Exertional heat stroke (EHS) usually occurs during or immediately after strenuous exercise and under extreme environmental conditions. Much of our clinical experience comes from the military and concerns physically fit and well-trained athletes. Even if the pathophysiology of EHS is not fully understood, it is not surprising that EHS can occur in poorly conditioned athletes performing unusual extreme physical activity under extreme environmental conditions.[1] Examples involving well-trained and heat-acclimatized athletes (without any previous illnesses) under unremarkable physical exercise or environmental conditions are much more difficult to explain. Therefore, a possible association between EHS and malignant hyperthermia (MH) could be explored, especially in light of their comparable clinical features (sometimes leading rapidly to multiorgan failure) and similar known pathophysiology (ie, hypermetabolic state; accelerated oxidative, chemical, and mechanical stress on muscle; and an uncontrolled increase in intracellular calcium).[2,3] An inherited subclinical myopathy, MH is characterized by a hypermetabolic reaction during anesthesia (volatile inhaled anesthetics or succinylcholine or both) associated with various mutations in the *RYR1* gene, encoding the skeletal muscle calcium release channel of the sarcoplasmic reticulum, also known as ryanodine receptor type 1.[4] The purpose of our report is to describe the clinical association of an MH mutation in the *RYR1* gene (p.K1393R) and EHS in an athlete, suggesting an association between these 2 acute and life-threatening disorders.

CASE REPORT

A previously healthy 30-year-old male athlete (semiprofessional rugby player) collapsed with initial seizures after a 10-km community running race of 48 minutes (ambient temperature and hygrometry were 21°C and 64%, respectively). Initial onsite evaluation showed an altered level of consciousness (Glasgow Coma Scale score of 3), hyperthermia (rectal temperature = 40.2°C), and sinus tachycardia (171 beats per minute). Arterial blood pressure was 90/50 mm Hg, and oxygen saturation was 95% while inhaling ambient air. Within 20 minutes of collapse, the athlete received intravenous fluid resuscitation and intubation; he was adequately monitored, cooled (with rotating ice bags), and immediately transported to the intensive care unit. On admission, he presented with recurrent vomiting and diarrhea. Laboratory analysis showed multiple organ failure with lactic acidosis (pH = 7.25 [normal = 7.35–7.45], lactate = 2.9 mmol/L [normal = 0.5–1.3 mmol/L]),

moderate rhabdomyolysis (creatine phosphokinase = 16210 U/L [normal = 38–174 U/L]) associated with hyperkalemia (6.39 mmol/L [normal = 3.5–5.3 mmol/L]), acute kidney failure (serum creatinine = 222.7 μmol/L [normal = 61.9–115 μmol/L], estimated glomerular filtration rate = 34 mL/min/1.73 m^2 [normal = 100–130 mL/min/1.73 m^2]), hepatocellular insufficiency (alanine aminotransferase = 3861 U/L [normal = 5–30 U/L], aspartate aminotransferase = 5256 U/L [normal = 5–30 U/L], factor V level = 13%), and disseminated intravascular coagulation (platelet count = 32.10^3/μL [normal = 150–400 10^3/μL], prothrombin = 18%, fibrinogen = 0.73 g/L [normal = 1.8–4 g/L]). Blood sodium concentration was preserved at 141 mmol/L (normal = 135–145 mmol/L).

Cooling was continued, fresh frozen plasma was administered, and intensive rehydration was provided, which allowed the patient to be extubated within 24 hours. Clinical symptoms and laboratory values progressively recovered, and after 5 days, the patient was transferred to the internal medicine department for further investigation. Medical questioning revealed no risk factors predisposing him to the development of exertional heat illness.

At 8 weeks after the collapse, the athlete was fully recovered, both clinically and according to laboratory values. He performed a maximal exercise challenge test based upon an incremental cycling protocol (room temperature = 21.7°C, hygrometry = 47%, pressure = 735 mm Hg; initial workload of 25 W increased by 25 W every minute until exhaustion). The results showed moderate exercise intolerance with a maximal heart rate of 187 beats per minute (93% of predicted), maximum minute power of 200 W (77% of predicted), and maximal oxygen uptake of 32.4 mL/min/kg (67% of predicted). No exercise-induced hyperthermia was demonstrated: rectal temperatures were 37.4°C and 37.6°C, respectively, before and after the exercise test. However, the oxidative metabolism of muscle was abnormal, involving excessive lactic acidosis (pH = 7.21, blood lactate = 10.8 mmol/L) and an early lactate threshold (reached at a power of 75 W, 29% of predicted).

The athlete provided informed written consent for genetic analysis of the *RYR1* gene. A targeted mutational analysis was performed for mutations previously reported in association with MH. A heterozygous missense variation p.K1393R was identified. The final diagnosis was established based on EHS with rhabdomyolysis associated with MH susceptibility. The athlete was given appropriate information about preventing exertional heat illness and advised to seek medical attention if he became symptomatic. He was allowed to progressively return to sport competition.[1]

DISCUSSION

Exertional heat stroke and MH are acute and life-threatening disorders that share comparable clinical features. An association between EHS and MH is supported by reports of EHS occurring in well-trained and acclimatized patients in the absence of any extreme environmental conditions or physical activity.[2,3] The most cited evidence of such an association was reported by Tobin et al,[5] who described the death of a 12-year-old boy with known MH after he developed EHS while playing football in mild weather (26°C). Postmortem genetic analysis revealed a known MH-associated p.R163C mutation in the *RYR1* gene, which led the authors to conclude that the MH was not associated with anesthetic agents.

In our case, the patient was a well-trained athlete. Since at least 2002, he had participated in 10 to 12 hours/week of sport (rugby, swimming, running, and cycling) without any particular complaints. Environmental conditions and intensity of physical activity were unremarkable at the time the athlete collapsed, thereby supporting a possible link between EHS and MH. This link was initially proposed because of abnormal results of in vitro pharmacologic muscle testing with caffeine and halothane,[6] and DNA-based screening for mutations of the *RYR1* gene suggested an association between EHS and MH.[7] The sequence variation of the *RYR1* gene (p.K1393R) found in our patient has already been documented as independently associated with either MH[8] or exertional rhabdomyolysis,[9] but to our knowledge, MH and exertional rhabdomyolysis have never been found to be associated. Functional tests on B cells harboring the p.K1393R mutation identified amino acid substitutions that alter intracellular calcium homeostasis and are most likely the cause of MH.[8] However, this variation is described in the general population with a minor allele frequency of 0.5% (rs137933390), and the possibility that it is a rare polymorphism cannot be excluded. Therefore, we need to carefully investigate individuals who experience EHS, especially in temperate climates or when there are no other predisposing factors.[2]

Regarding the high concentrations of lactate during early exercise observed in patients with MH,[10] incremental exercise testing may be helpful when MH is suspected, although no formal guidelines currently exist. In our case, the patient presented with abnormal oxidative metabolism of muscle, exaggerated peak lactate levels, profound lactic acidosis, and early lactate threshold at maximal exercise challenge.[10] This last oxidative metabolism abnormality is thought to lead to sympathetic stimulation with subsequent free fatty acid liberation and reduced skin blood flow,[10,11] resulting in thermoregulatory failure and MH.[2]

Most people recover completely from EHS within a few weeks by following common-sense recommendations for returning to sport (ie, no clinical symptoms, normal laboratory findings, gradual return to basal exercise performance).[1,12] However, the return-to-play decision for a patient who has EHS associated with MH susceptibility is more complex because of the small number of reports and the near impossibility of conducting systematic investigations. Therefore, no guidelines are currently available, but lifestyle and physical activity should probably not be modified.[13] Although minimal evidence indicates that exertion should be limited in patients with MH, they should still be appropriately informed and educated about preventive strategies and the importance of seeking medical attention if symptoms develop.

CONCLUSIONS

The common features of EHS and MH suggest an association between these acute and life-threatening disorders. If treated promptly and cooled aggressively, most people recover completely from EHS within a few weeks, which supports current return-to-play guidelines.[12]

An emerging body of evidence now suggests that EHS could be associated with MH, raising questions about the management (ie, diagnosis, treatment, return to play) of a patient with both conditions. To our knowledge, this is the first description of this MH mutation in the *RYR1* gene (p.K1393R) associated with EHS. Further clinical and laboratory research is needed to clarify the possibly associated pathophysiologic mechanisms between these disorders.

REFERENCES

1. Casa DJ, Armstrong LE, Kenny GP, O'Connor FG, Huggins RA. Exertional heat stroke: new concepts regarding cause and care. *Curr Sports Med Rep*. 2012;11(3):115–123.
2. Grogan H, Hopkins PM. Heat stroke: implications for critical care and anaesthesia. *Br J Anaesth*. 2002;88(5):700–707.
3. Capacchione JF, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. *Anesth Analg*. 2009;109(4):1065–1069.
4. Riazi S, Kraeva N, Muldoon SM, et al. Malignant hyperthermia and the clinical significance of type-1 ryanodine receptor gene (RYR1) variants: proceedings of the 2013 MHAUS Scientific Conference. *Can J Anaesth*. 2014;61(11):1040–1049.
5. Tobin JR, Jason DR, Challa VR, Nelson TE, Sambuughin N. Malignant hyperthermia and apparent heat stroke. *JAMA*. 2001; 286(2):168–169.
6. Wappler F, Fiege M, Steinfath M, et al. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology*. 2001;94(1):95–100.
7. Carsana A. Exercise-induced rhabdomyolysis and stress-induced malignant hyperthermia events, association with malignant hyperthermia susceptibility, and RYR1 gene sequence variations. *Sci World J*. 2013;531465.
8. Vukcevic M, Broman M, Islander G, et al. Functional properties of RYR1 mutations identified in Swedish patients with malignant hyperthermia and central core disease. *Anesth Analg*. 2010;111(1): 185–190.
9. Dlamini N, Voermans NC, Lillis S, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. *Neuromuscul Disord*. 2013;23(7):540–548.
10. Vanuxem P, Vanuxem D, Raharison L, Aubert M, Pouliquen G, Deslangles O. Maximal exercise and muscle energy metabolism after recovery from exercise hyperthermia syndrome. *Muscle Nerve*. 2001; 24(8):1071–1077.
11. Campbell IT, Ellis FR, Evans RT, Mortimer MG. Studies of body temperatures, blood lactate, cortisol and free fatty acid levels during exercise in human subjects susceptible to malignant hyperpyrexia. *Acta Anaesthesiol Scand*. 1983;27(5):349–355.
12. Armstrong LE, Casa DJ, Millard-Stafford M, et al. American College of Sports Medicine position stand: exertional heat illness during training and competition. *Med Sci Sports Exerc*. 2007;39(3):556–572.
13. Hopkins PM. Is there a link between malignant hyperthermia and exertional heat illness? *Br J Sports Med*. 2007;41(5):283–284.

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