Is there a link between malignant hyperthermia and exertional heat illness?

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Malignant hyperthermia is a relatively rare pharmacogenetic disorder inherited in an autosomal dominant fashion.¹ It is triggered in previously healthy susceptible individuals by exposure to potent inhalational anaesthetic agents and the muscle relaxant succinylcholine (succinylcholine). The clinical features of a malignant hyperthermia reaction have many similarities to those of heat illness.² These include a mixed respiratory and metabolic acidosis, tachycardia, rhabdomyolysis and muscle rigidity with progressive hyperthermia. The condition acquired its name because of the high mortality of the early cases.

Exertional heat illness occurs mainly in previously healthy young men during exercise, often in hot and humid climates to which the victim is not properly acclimatised.³ Typical scenarios include military exercises undertaken by personnel recently arrived in a hot country, and long-distance races that happen to coincide with one of the first hot days of the year. In these situations, multiple cases are common. Exertional heat illness is also more likely in the obese, in the physically unfit, in the presence of concurrent viral infection, after recent alcohol consumption, in those with skin diseases preventing sweating, in those with thyrotoxicosis and in those taking a variety of prescribed or non-prescribed medicines.⁴ There are, however, sporadic cases that occur in individuals, with no obvious predisposing factors, exercising in unremarkable weather conditions. Again, these often occur in the context of military exercises or running races, but it is notable that the victim is the only person out of tens, hundreds or even thousands of others taking part to be so affected. It is these cases that arouse particular suspicion of an underlying, relatively rare, predisposing factor.

Malignant hyperthermia is caused by a defect in skeletal muscle intracellular calcium homeostasis. Clinical diagnosis of susceptibility to malignant hyperthermia

is based on in vitro pharmacological responses of freshly excised skeletal muscle specimens when exposed to the anaesthetic halothane and other compounds. The drug-evoked contractile responses are measured as a surrogate of intracellular calcium concentration. More recently, there has been a limited introduction of DNA-based testing through screening for mutations of the ryanodine receptor 1 (*RYR1*) gene. The *RYR1* gene encodes the calcium release channel of the skeletal muscle sarcoplasmic reticulum and is the major gene implicated in malignant hyperthermia susceptibility.⁵ However, there is locus and allelic heterogeneity of malignant hyperthermia and a likely causative genetic defect has not been identified in the majority of cases.

The possibility of a link between malignant hyperthermia and exertional heat illness is not new.⁶ Indeed, porcine malignant hyperthermia, which is caused in all cases by an *RYR1* gene mutation, is associated with awake episodes triggered by physical exertion in addition to anaesthetic-induced reactions.

There have been several reports of patients with a history of exertional heat illness who have fulfilled the laboratory diagnostic criteria for susceptibility to malignant hyperthermia.⁷⁻¹⁰ These reports relate to the in vitro pharmacological muscle tests. Such findings have been reported from workers in Austria,⁷ Germany¹⁰ and France⁹ in addition to cases from my own unit.⁸ The cases we reported involved tests on both the patients and their first-degree relatives. Interestingly, we found abnormal responses in one parent in each case in addition to the patient.⁸ These cases provided the first direct evidence of an inherited skeletal muscle abnormality in survivors of exertional heat illness. They did not, however, enable us to infer that the defect was the same as that underlying malignant hyperthermia. Nor was it possible to extrapolate these findings to imply increased risk of malignant hyperthermia

under anaesthesia from a history of exertional heat illness or vice versa.

Wappler and colleagues¹⁰ studied a group of German individuals with a history of exertional rhabdomyolysis, which has been suggested to predispose to exertional heat illness.¹¹ Eleven out of 12 exertional rhabdomyolysis patients had abnormal in vitro pharmacological muscle test responses and three of these patients were found to have *RYR1* mutations.¹⁰ Perhaps of even greater significance, Tobin *et al*¹² reported the tragic case of a 12-year-old boy who survived a malignant hyperthermia reaction during anaesthesia but who subsequently died of exertional heat stroke following a game of football. DNA analysis of the child and his father revealed a mutation in the *RYR1* gene that had previously been associated with malignant hyperthermia.

One of Wappler's patients with exertional rhabdomyolysis who was found to have an *RYR1* mutation was further investigated for exercise-induced hyperthermia.¹³ In addition to rhabdomyolysis he complained of fever induced by "stress" or minimal exercise. His response to a graded exercise protocol was notable for a profound lactic acidosis. Vanuxem *et al*¹⁴ have also demonstrated increased lactate production during exercise in survivors of exertional heat stroke. These workers also reported increased free fatty acid production but not utilisation and increased core temperature with a delayed rise in peripheral temperature in their subjects. They concluded that their subjects had an abnormality in muscle oxidative metabolism leading to sympathetic stimulation with subsequent free fatty acid liberation and reduced skin blood flow. Interestingly, Campbell *et al*¹⁵ reported almost identical findings in a group of malignant hyperthermia susceptible subjects.

Parallels between muscle metabolism in malignant hyperthermia and exertional heat stroke have also been found using ³¹P magnetic resonance spectroscopy.^{9, 16} Here, early muscle pH changes during exercise (especially aerobic exercise) are greater in malignant hyperthermia and exertional heat stroke subjects than in controls. In the presence of normal muscle proton handling and phosphocreatine utilisation, these changes are taken to show increased glycolytic activity secondary to, for example, increased cytosolic calcium concentration. These findings are entirely consistent with the exercise studies of Vanuxem *et al*¹⁴ and Campbell *et al*,¹⁵ in which the sympathetic hyperactivity is consistent with excessive pyruvate presentation to the mitochondria, rather than absolute reduced mitochondrial oxidative capacity.

My interpretation of this evidence and collection of case reports is that a

minority of episodes of exertional heat illness occur in individuals with an underlying predisposing skeletal muscle defect. Individuals who experience exertional heat illness, especially repeated episodes, in a temperate climate and without other predisposing factors are most likely to have such a muscle defect. Such individuals referred to the UK Malignant Hyperthermia Investigation Unit in Leeds are offered malignant hyperthermia screening tests. When these tests are positive, they are advised to avoid prolonged, severe exercise, to be treated as susceptible to malignant hyperthermia during anaesthesia and to warn family members that they may be similarly at risk. Family members are offered appropriate screening.

Behavioural modification may account for the paucity of individuals susceptible to malignant hyperthermia reporting exercise-related symptoms. Among our malignant hyperthermia patients we have several professional sportsmen and elite athletes, but it may be relevant that their prowess is almost exclusively confined to power/sprint events rather than predominantly endurance events. It may also be the case that only some of the genetic defects that predispose to malignant hyperthermia result in sufficiently increased calcium cycling under physiological conditions to predispose to exercise-related symptoms. For these reasons we do not advise patients to modify their lifestyle when diagnosed with susceptibility to malignant hyperthermia.

Finally, I would like to address whether the link between some cases of exertional heat illness and malignant hyperthermia has any implications for the use of dantrolene in the treatment of exertional heat stroke. In theory, dantrolene would be of benefit in any condition where excessive heat generation by skeletal muscles contributes to a high body temperature.¹⁷ This is irrespective of whether the cause is a primary muscle defect, or is secondary to excessive muscle activation as in neuroleptic malignant syndrome or sepsis. Indeed, dantrolene is remarkably effective in lowering body temperature in all these circumstances. Dantrolene is not useful, however, in classical heat stroke where the heat gain is from the environment and the evidence supports this. It is wrong, however, to extrapolate this evidence to exertional heat stroke.¹⁸

Despite the theoretical benefits of dantrolene in exertional heat stroke, the question of its use is somewhat academic

as its provision in the field, where it would best be utilised, is impractical. The mainstay of treatment of exertional heat stroke will remain aggressive cooling and intravenous fluid resuscitation instituted, if possible, before transfer to hospital. If, despite these measures, the patient's core temperature is $>39^{\circ}\text{C}$ on admission to hospital, and/or there is overt muscle rigidity unrelated to seizure activity and/or hyperkalaemia, I would recommend administration of dantrolene intravenous in a dose of 2.5–3 mg/kg. All these features are poor prognostic indicators and warrant every tangible therapeutic option: short-term use of dantrolene has not been associated with hepatic impairment, while temporary muscle weakness can easily be managed by ventilatory support if necessary (if it has not already been implemented).

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COMMENTARY

Exertional heat illness and malignant hyperthermia (MH) are acute and life-threatening disorders that share comparable clinical features, such as tachycardia, rhabdomyolysis and hyperthermia. Therefore, in several case reports, a possible link between both has been discussed. However, the number of these reports is small and systematic investigations nearly impossible. This review presents all relevant aspects of MH and exertional heat illness. Furthermore, the author discusses the association between both disorders. The main conclusions are as follows: (1) only a minority of patients with an exertional heat illness have an underlying skeletal muscle defect; (2) most patients with MH should not modify their physical activity; and (3) only those patients with exertional heat stroke not responding to symptomatic therapy should be treated with dantrolene. These conclusions can be supported completely; however, it would be desirable to develop guidelines for investigating patients with exertional heat illness, especially with respect to MH susceptibility.

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