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CASE REPORT

The heat is on: Acute liver failure caused by exertional heatstroke

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Abstract

We present a case of a 30-year-old man who developed exertional heatstroke which was complicated by liver failure. He was transferred to our centre for a possible liver transplantation but unfortunately succumbed to multiorgan failure. In a review of literature we discuss the diagnosis and treatment of heatstroke, the possible underlying pathophysiology and overlap with malignant hyperthermia.

Introduction

Heatstroke is defined as a core temperature exceeding 40.0°C combined with central nervous system dysfunction. Other organ dysfunction can also occur. A patient with heatstroke can present with mild symptoms but may also present directly with severe multiorgan failure.[1] In the summer of 2003, Paris experienced such a severe heat wave that 1465 patients with heat-related illness presented to a hospital. This led to 72 intensive care admissions and in affected individuals the one-year survival was only 57%, even though a proportion of these patients primarily presented with only mild symptoms.[2] Exertional heatstroke is a variant of heatstroke which is induced by exercise. Case reports and series show that this exercise need not always push the boundaries of someone's exercise tolerance, though a warm environment increases the risk. Considering the predictions for climate change we may see an increase in hospital admissions for heat-related illness and heatstroke in the coming decades.[3] It may therefore become increasingly relevant to solidify our knowledge about this condition.

Case history

A 30-year-old man was found unconscious along the roadside while participating in an outdoor athletic event with an ambient temperature of just over 30°C and no shade from the sun along the track. He was estimated to have run a distance of 8 km from the starting point. Upon presentation to the local emergency department his airway was found unobstructed and his respiration stable. He was hypotensive at 50/30 mmHg with a pulse rate of 150/min. His Glasgow Coma Scale (GCS) was determined as E1M1V1. His body temperature was 41.8°C. Because of suspected exertional heatstroke and associated encephalopathy his body temperature was actively and effectively lowered to 38.5°C and he was admitted to the ICU. At first he regained consciousness but in the following two days his condition deteriorated due to acute liver failure with associated lactic acid acidosis and respiratory insufficiency for which intubation and mechanical ventilation was initiated. Subsequently he developed acute renal failure, perhaps partially due to moderate rhabdomyolysis *(figure 1)*, and diffuse intravascular coagulation.

On day 3 he was referred to our ICU because of the potential need for high urgency liver transplantation. By then his concomitant kidney failure due to acute kidney injury required renal replacement therapy. On day 5 a liver offered for transplantation was rejected firstly because the patient's liver failure appeared to be recovering and secondly because the transplant organ offered showed signs of steatosis hepatis. Unfortunately, hereafter the patient showed no signs of regaining any normal liver function *(figure 1)*. When on day 10 another liver transplant was offered, we were forced to decline due to spontaneous bacterial peritonitis. On day 15 a third liver transplant was accepted. However, when on the operating table the transplant surgeons found the patient was suffering from necrotising pancreatitis. An abdominal computed tomography from the previous evening gave the suggestion of an oedematous pancreas, though the pancreas region was poorly assessable, and the possibility of an open-and-shut procedure had been discussed with the family. The pancreatitis was considered secondary to his acute liver failure and systemic inflammatory response syndrome (SIRS). While waiting for his pancreatitis to subside to be able to once more activate his status on the high urgency transplant list he developed septicaemia on day

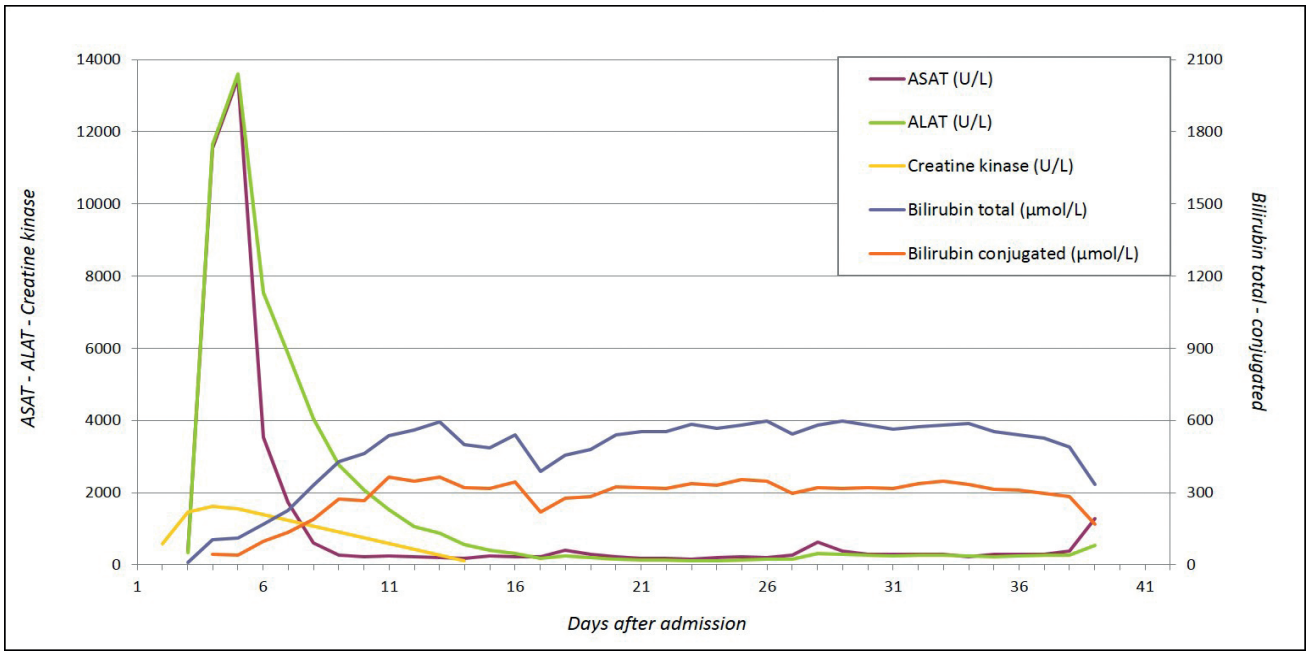


Figure 1. Trends of serum transaminases and bilirubin levels during hospitalisation of our patient
The left Y-axis refers to ASAT, ALAT and creatine kinase levels in U/l, the right Y-axis refers to bilirubin levels, both total and conjugated, in µmol/l

26 with a suspected bowel perforation. No perforation could be identified on laparotomy. In the postoperative period a severe inflammatory response caused excessive haemodynamic instability for several days.

From the moment of his admission to our hospital he showed varying signs of hepatic encephalopathy for which we strived to reach a hyperosmolar state by increasing the sodium concentration of the continuous veno-venous haemofiltration substitution fluids. During his more stable periods we were able to withdraw sedation and while remaining on ventilatory support, he was awake and responsive to his surroundings and able to communicate in a simple yes/no form. On day 38 a fourth liver transplant was offered that we once again were forced to decline due to a recurrence of severe haemodynamic instability, this time most likely attributable to his continued liver failure. On day 40 his shock and multiorgan failure were refractory and he developed hypoglycaemia for which continuous glucose infusion was necessary. We found we would no longer be able to bring him back into a condition where he would be transplantable and he unfortunately passed away.

Permission was granted for post-mortem examination of the abdominal organs, which showed extensive ductal proliferation and transformation in the liver, reactive ductal changes and acinar cell necrosis of the pancreas, and calcifying necrosis of striated muscles attributed to heatstroke.

Our patient was not the only person taken ill during this particular outdoor athletic event. However, his case was the only reported fatality. This left us wondering why this patient presented with such severe symptoms including his refractive liver failure. Could there be link with other hyperthermic and heat-related illnesses?

Discussion

The Japanese Association of Acute Medicine has proposed a novel classification of heat-related illness identifying three stages of severity with varying symptoms *(figure 2)*.[1, 4] This classification appears useful in determining the interventions necessary. In all stages, lowering core temperature is paramount and a more aggressive approach even at stage I seems justified to prevent life-threatening complications. Cooling methods previously described include immersion, evaporation or bladder, gastric and rectal lavage. The efficacy of one cooling method over the other has not been proven, but a target rectal temperature of 39.5°C appears safe. However, aural and even rectal temperature measurement may underestimate the core temperature, particularly when cooling methods have been initiated. It is therefore recommended to switch to invasive temperature measurement via a central venous catheter, requiring admission to a high or intensive care unit.[1]

Acute liver failure occurs relatively frequently in heatstroke, and hypophosphataemia upon presentation appears to predict the occurrence of acute liver failure.[5] In this series of 25 patients with acute liver failure in heatstroke, three patients died and the remaining patients made a full recovery without the need for transplantation. We could not find any figures on how often acute liver failure in heatstroke may lead to liver transplantation, but several case reports describe this.[6, 7] Conversely in a large case series of acute liver failure patients (2675 patients) eight were diagnosed with heatstroke as the culprit.[8] Coinciding pancreatitis was not explicitly mentioned in the case reports and series. Whether the pancreatitis seen in our patient could be attributed directly to his heatstroke or

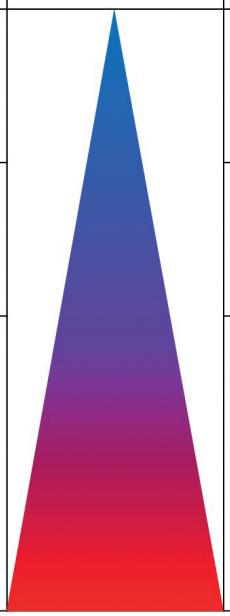
In hyperthermic patients:	Symptoms	Severity	Treatment	Classification from clinical presentations	Notes on triage
Stage I (first aid and observation at the scene)	Feeling faint, dizzy. Muscle pain, cramps, stiffness. Heavy sweating. GCS 15		Rest in a cool place. Cooling body surface with ice packs or ice bath. Oral rehydration.	Heat cramp Heat syncope	First aid at the scene sufficient only when symptoms improve.
Stage II (referral to medical institution)	Headache, vomiting, fatigue, sinking feeling, impaired attention and judgement. GCS 14		Body temperature management. Intravenous rehydration when oral intake is insufficient.	Heat exhaustion	Referral to hospital at Stage II or when Stage I symptoms fail to improve with first aid at the scene.
Stage III (inpatient hospital care)	Includes at least 1 of: CNS manifestation: GCS <14, cerebellar dysfunction, seizures. Hepatic or renal dysfunction either at presentation or during hospital stay. Diffuse intravascular coagulation.		Body temperature management with internal cooling adjacent to body surface cooling. Respiratory and circulatory support including rehydration. Renal replacement therapy as needed. Monitoring and transfusion for bleeding complications as needed.	Heatstroke	Stage III may be determined by ambulance staff, at examination at the emergency department or during follow up after admission. Intensive Care monitoring and support is advised.

Figure 2. Overview of symptoms, classification and treatment recommendations for heat related illness

Adapted from Japanese Association of Acute Medicine Heat Related Illness Classification 2015 as evaluated by the Heatstroke STUDY 2012[1, 4]
GCS = Glasgow Coma Scale; CNS = central nervous system

should be seen as a complication of his acute liver failure and SIRS, cannot be determined. Our patient showed a pronounced initial elevation of transaminases. Their fall was initially attributed to the start of recovery. However, as shown in figure 1, his serum bilirubin continued to rise and plateaued at around 550 µmol/l. The lowering of transaminases and associated rise in bilirubin usually indicates a severe loss of hepatocytes and is associated with a lack of recovery of any meaningful liver function. The pathophysiological mechanism of heatstroke has not been completely elucidated. In non-exertional heatstroke an incompletely understood disturbance in thermoregulation leads to an increased body temperature. This effect is compounded by dehydration and salt depletion, when the necessary increase in cardiac output cannot be achieved. At a core temperature of over 42°C oxidative phosphorylation becomes uncoupled and metabolic demand can no longer be met. This also undermines thermoregulatory mechanisms exacerbating the issue further. Normally, an increase in body temperature should induce the expression and/or activation of heat shock proteins that

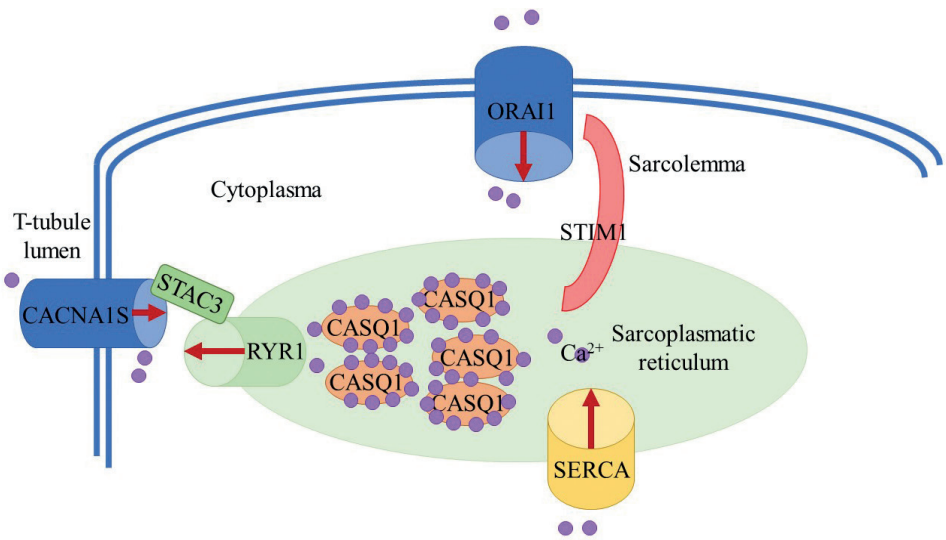


Figure 3. Calcium homeostasis of the muscle fibre with candidate genes associated with malignant hyperthermia. Calcium is stored in the sarcoplasmatic reticulum, bound to calsequestrin (coded by CASQ1). When the arrival of the action potential activates the dihydropyridine receptor (DHPR coded by CACNA1S), the receptor opens and allows calcium influx into the cell. Activation of DHPR also leads to activation of RYR1 inducing calcium release from the sarcoplasmatic reticulum (SR). Calcium stores in the SR are released from calsequestrin. Calcium depletion of the SR activates stromal interaction molecule 1 (coded by STIM1) which unfolds through the cytoplasm to bind to calcium release-activated modulator 1 (coded by ORAI1). This transmembranous channel also facilitates calcium influx into the cytoplasm. There calcium binds to troponin and induces contraction. Note: all proteins are labelled by their encoding genes

protect cells from heat-induced apoptosis. When the activity of heat shock proteins is insufficient, damage is caused via two pathways. Muscles producing interleukin-1 and -6 and leakage of endotoxins from the intestine induce an inflammatory response with activation of neutrophilic granulocytes and monocytes. Protein C, S and antithrombin III activity is reduced leading to an increased activation of thrombin and clot formation that can escalate to diffuse intravascular coagulation.[1, 9, 10]

Exertional heatstroke, in contrast to spontaneous heatstroke, also presents with muscle fibre damage as evidenced by signs of rhabdomyolysis. The full clinical picture of exertional heatstroke includes encephalopathy, rhabdomyolysis, renal failure, acute liver failure, respiratory compromise, myocardial injury and intestinal ischaemia. This list shows considerable overlap with clinical symptoms of malignant hyperthermia.[11, 12] The idea of commonality between exertional heatstroke and malignant hyperthermia is not new.[13] In malignant hyperthermia intracellular calcium homeostasis in skeletal muscles is disrupted on exposure to an extracorporeal substance, most commonly halothane-derived inhalation anaesthetics, though depolarising muscle relaxants may also serve as a trigger. In normal muscle fibre activation, calcium is released from the sarcoplasmatic reticulum into the myoplasm through the ryanodine receptor to induce muscle fibre contraction. Upon exposure to, for example, a halothane ether, an excess quantity of calcium is released inducing muscle rigidity, heat production by increased ATP use and rhabdomyolysis through breakdown of the sarcolemmal membrane.[14] The most commonly known gene mutations associated with malignant hyperthermia are located on the ryanodine receptor 1 (RYR1); however, more novel mutations have been found.[15, 16] Indeed, when observing the intracellular pathway of calcium release more candidate genes may be associated *(figure 3)*. When a patient is suspected of malignant hyperthermia an in vitro contracture test (IVCT) may identify susceptibility to it, though this requires a relatively invasive muscle biopsy.[17] In a cohort of military personnel almost half the subjects showed a positive result on the IVCT after experiencing an episode of exertional heatstroke.[18] Variants of RYR1 have been identified in patients after an episode of exertional heatstroke.[19, 20] Calsequestrin-1 (CASQ1) is a calcium-binding protein located in the sarcoplasmatic reticulum and has been suggested as a candidate gene associated with malignant hyperthermia. In a model of CASQ1 knockout mice, these mice showed an increase in spontaneous mortality and susceptibility to malignant hyperthermia and heat stress.[15] These publications show an active interest in exertional heatstroke and malignant hyperthermia and a potential genetic predisposition in patients developing it, though more conclusive trials have yet to be published. Unfortunately, we were not aware of the potential link between heatstroke and malignant hyperthermia before our patient passed away. Attempts to isolate DNA for gene sequencing from post-mortem tissues failed to yield stable DNA strands. DNA analysis from his sister showed no known pathogenic variants in RYR1 or CACNA1S (encoding the dihydropyridine receptor or DHPR) genes, though of course it does not follow that her brother, our patient, did not carry one.

Conclusion

Here we present a case of exertional heatstroke complicated by liver failure with fatal outcome. Immediate lowering of the core body temperature is paramount in the early management of heatstroke. Liver failure in heatstroke may be so severe as to warrant liver transplantation. Susceptibility to malignant hyperthermia may intersect with susceptibility to exertional heatstroke since the same genetic associations seem to be involved.

Disclosures

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