Heat-Exercise Hyperpyrexia

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SUMMARY: A fatal case of "heat stroke" occurring on exercise in temperate conditions is described. Possible mechanisms for increased susceptibility are discussed and attention is drawn to a possible overlap with the malignant hyperpyrexia (MH) syndrome. The second day of strenuous exercise may be a time of special risk. More frequent consideration of dantrolene treatment in heat injury is suggested and the term "heat-exercise hyperpyrexia" is proposed to replace "heat stroke" and "exertional hyperpyrexia".

Introduction

With some exceptions such as the deaths that occur in elderly and undernourished people each year in Indian trains, there is invariably an element of exertion involved in cases of heat stroke. The clinical, laboratory and autopsy findings of exertional hyperpyrexia are identical with those of heat stroke, and different papers, somewhat confusingly, use these terms and variants of them interchangeably^{1,2}. From simple physical and physiological principles, the risk of heat injury is increased both by exercise, which increases heat production, and by raised environmental temperature and humidity, which reduce heat loss. Other important factors which influence the balance of heat production and loss are clothing, drugs (such as anticholinergics, phenothiazines and diuretics), alcohol, fluid intake, body weight, direct sunlight, acclimatisation to heat and the presence of other febrile illness^{3,4}. However, when account is taken of all these variables, there remains the impression that some individuals are exceptionally susceptible to the effects of exercise and heat. The tragic death of one such man is described below.

Case Report

The patient was a white, 21 year old infantry private belonging to the contingent of another army serving with the United Nations Force in Cyprus. He had been treated a year previously in his home country after collapsing with "heat stroke" on a Battle Fitness Test in moderate conditions, but details are not available. On 19 April 1988 he successfully completed the first half of a 2 day Battle Fitness Test involving a 10 mile forced march at a planned pace of 12 minutes/mile. In fact, because his platoon lost their way, they actually covered about 12 miles. Dress was tropical combat kit with soft hat, webbing and weapon. The second half of the test was identical and began at 0530 hours on 20 April. Measurements at nearby Nicosia airport at 0700 hours local time gave a dry bulb air temperature of 12°C (53.6°F) and humidity of 88%. A light rain was falling. Eight miles into the march he was found to be confused and was lagging behind. He soon collapsed. On arrival at the local medical centre about 30 minutes later he was

unconscious, hot and had no evidence of sweating. Axillary temperature was 40.5°C, respiration was laboured and his BP was 60/40mm Hg. He was cooled with ice packs and given intravenous fluids. Sweating was noted at 0930 hours and he regained consciousness at 1000 hours, but his temperature was still 39°C. At 1300 hours he had 4 or 5 grand mal convulsions which were treated with diazepam, naloxone and haloperidol. At 1630 hours, after transfer to hospital, his cardiovascular state was satisfactory and his BP was 90/70mm Hg. Although he initially responded to simple commands, he soon lost consciousness again. He was treated with dexamethasone, cimetidine and intravenous fluids but next day he was worse with bilateral ankle clonus, transient changes in pupil size and evidence of diffuse intravascular coagulation (DIC). Aeromedical evacuation to UK was arranged.

On arrival, he was unresponsive to voice but did respond to pain. The arms were flaccid but there was bilateral ankle clonus and plantar reflexes were extensor. There were no cranial nerve signs and optic fundi could not be seen. Jaundice was noted. Urine output remained satisfactory. Tests done in Cyprus and in UK showed thrombocytopenia (lowest $25 \times 10^9/l$), bilirubinaemia (increasing to 357 mmol/l), increased transaminases (over 14,000 iu/l), creatine phosphokinase (17,850 iu/l) and lactic dehydrogenase 1,656 iu/l, prolonged prothrombin time (272 seconds), increased fibrinogen degeneration products (160 µg/dl), low blood urea (1.5 mmol/l) and only minor abnormalities of serum creatinine, alkaline phosphatase and serum albumin. White cell count $16.6 \times 10^9/l$. Chest X-ray, ECG, spinal fluid, CT scan of brain and initial blood gases were normal and blood was negative for malaria parasites. Serological tests for hepatitis A and B were negative.

His prognosis was considered to be extremely poor, especially as he continued to deteriorate with increasing jaundice, diminishing response, increasing pulse rate, variable but generally dilating pupils, and eventually decreased urine output, noisy respiration, falling arterial oxygen pressures and rising carbon dioxide pressures. He died at 1710 hours on 25 April.

Autopsy findings

At post mortem, external examination showed the body of a heavily built young man with jaundice, oedema and priapism. The brain was oedematous and there was a small haemorrhage in the cerebellum. Both lungs showed extensive haemorrhagic pneumonia but without frank pus. There was a slight pericardial effusion and the heart showed a subendocardial haemorrhage and some petechiae. The liver was soft and friable, the spleen was congested and also friable, and the kidneys were slightly oedematous. The cause of death was certified as haemorrhagic bronchopneumonia and hepatic failure due to hyperthermia. Histopathology added little except that sweat glands were normal in number and architecture and the liver showed severe centrilobular necrosis and intrahepatic cholestasis.

Discussion

Because of the relatively low environmental temperature at which this illness occurred, efforts were made to find an alternative diagnosis to that of heat stroke. Hepatitis A and B, meningitis and malaria were ruled out. In any case, the findings of DIC, thrombocytopenia, convulsions, and hepatic failure of sudden onset were highly suggestive of heat injury and the findings at autopsy provided strong corroboration⁵. The question remains as to why he should have suffered heat injury at a time when others were unaffected. A Summary Investigation by his own service established that he was of average fitness and did not take alcohol on the night before the test. There was a suggestion that he had "a bit of a cold" and he may have been taking an anticongestant but no container was subsequently found. He was certainly overweight (estimated Body Mass Index 28% (normal 20-25%) and he had made efforts to reduce this. He was not a new arrival in Cyprus, although the exact date of posting is not available. There were no irregularities in the conduct of the test, and the administration of first aid and the speed of evacuation were considered satisfactory.

This man did not have anhidrosis. He was almost certainly not taking any drug that impaired sweating and heat loss was not unduly prevented by inappropriate clothing. Humidity was, however, quite high at 88%. His history of collapse on the previous Battle Fitness Test and his final, fatal illness suggest that he was at the extreme end of the spectrum of susceptibility to the effects of exercise and heat.

This case is not unique in occurring in relatively mild conditions. Parnell and Restall⁶ described a fatal case after only 15 minutes forced marching at 16.7°C and 87% relative humidity, and Hanson *et al*⁷ report a severe collapse after running 10km at 16°C and 60% humidity. Such cases are sometimes called exertional hyperpyrexia¹, sometimes heat stroke^{6,7} and sometimes exertional heat stroke². Although anhidrosis is said to be present in exertional hyperpyrexia and absent in heat

stroke¹, this is not a consistent difference and the present case certainly lacked sweating on initial examination and resumed sweating with treatment.

Hyperpyrexia is a common and important problem in military medicine. Henderson *et al*³ documented 19 severe cases in a Hong Kong summer and even in Aldershot there were 40 admissions from heat-related illness in 38 months⁶. Training in inappropriate clothing has led to death¹ and this has caused public concern^{8,9}. The British Army uses the Wet Bulb Globe Temperature Index to control physical exercise in warm humid conditions³, but neither this nor any other current guidelines would have saved the patient described here.

The pathophysiological mechanisms in exertional hyperpyrexia have recently been well reviewed¹. A fall in plasma volume occurs due to fluid loss by sweating and probably also because there is a shift of fluid from the extravascular to the intravascular space because of the breakdown of glycogen to smaller and more osmotically-active molecules. This hypovolaemia may lead to a vasoconstriction that helps to preserve circulation but has the adverse effect of reducing heat loss through the skin. At a more advanced stage circulatory failure may lead to, or exacerbate, renal and hepatic failure. Meanwhile, however, the denaturation of protein due to unphysiological temperatures in tissues leads to direct injury. In the liver, this causes hepatic failure with possible encephalopathy, hypoglycaemia and impaired blood clotting. Muscle damage may be of even greater importance, leading to enzyme release, hyperkalaemia, hyperuricaemia, myoglobinaemia with resultant renal damage, and Rhabdomyolysis may also be the trigger for the DIC which commonly occurs. This causes hypofibrinogenemia, thrombocytopenia, further renal damage, multiple haemorrhages and the haemorrhagic pneumonia which often occurs as a terminal event^{1,5,10}. A recent study has, however, shown that thrombocytopenia may occur even in cases without DIC¹¹. Brain function may be impaired by direct thermal injury (causing convulsions and oedema), by hepatic encephalopathy, by hypoglycaemia and by haemorrhage.

In the present case, no measurements of myoglobin were made, but the very high creatine phosphokinase levels suggested severe muscle damage. Liver failure, DIC and cerebral oedema were prominent mechanisms but renal function was preserved until the last few hours of life.

Little has been written about the possible reasons why some individuals should be unduly susceptible to heat illness. They may simply have relatively inefficient homeostatic mechanisms or there may be a specific defect in the hypothalamus such that a rising core temperature is not detected or an appropriate response is not made. Another possibility is deficiency in the intracellular response to thermal threat, such as the production of heat shock proteins¹². In relation to this it is of interest that death occurred in this case as in two

other documented cases^{1,6}, on the second day of a strenuous test, thus raising the possibility that some such mechanism had been overstressed on the first day and had not had time to recover.

On the other hand, the possibility of excessive heat production might be considered. Attention has been drawn¹³ to similarities between heat stroke and malignant hyperpyrexia (MH) and it has been suggested that individuals susceptible to MH may also be susceptible to heat stroke. Malignant hyperpyrexia is well known to anaesthetists as a condition of autosomal dominant inheritance in which anaesthetic agents (most commonly halothane) cause fulminating hyperpyrexia and death occurs in about 70% of cases. The lesion responsible is thought to be a defect in muscle fibres, probably in the sarcoplasmic reticulum, leading to abnormalities in the intracellular flux of calcium ions, increased muscle contraction and therefore heat production¹⁴. Muscle can be tested *in vitro* for the defect, and affected muscle shows increased contractility on exposure to halothane or caffeine. In at least one case¹³ this abnormal response has been found in a subject who had recovered from heat stroke. Dantrolene sodium, a drug which acts in muscle to uncouple excitation and contraction, is useful in both treatment and prophylaxis of MH, although its exact mechanism of action is unknown¹⁴. In heat stroke, dantrolene has been dramatically successful in some clinical cases^{13,15}, but not in a canine model¹⁶.

Conclusion

This case report illustrates a Serviceman at the extreme end of a spectrum of susceptibility to the combined effects of environmental and exertional stress. Although training personnel should pay attention to all the adverse factors that have been described, it is doubtful, as with the effects of high altitude¹⁷, if any regulations can protect these very sensitive subjects. A high level of awareness and vigilance is required, particularly perhaps on the second day of strenuous exercise.

There is little justification for using the terms "heat stroke" and "exertional hyperpyrexia" in a mutually exclusive fashion. Clarity of thinking could be encouraged by using the term "heat-exercise

hyperpyrexia" and by identifying the factors chiefly responsible. In this case, they would be strenuous exercise and humidity, possibly associated with obesity, respiratory infection and the use of a decongestant. The patient may have had a predisposing condition, such as MH, and trial use of dantrolene might have been beneficial.

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