CASE REPORT

Exertional heat stroke and acute liver failure: a late dysfunction

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Accepted 25 February 2016

SUMMARY

Heat stroke (HS) is defined as a severe elevation of core body temperature along with central nervous system dysfunction. Exertional heat stroke (EHS) with acute liver failure (ALF) is a rare condition. The authors report the case of a 25-year-old man with a history of cognitive enhancers' intake who developed hyperthermia and neurological impairment while running an outdoor marathon. The patient was cooled and returned to normal body temperature after 6 h. He subsequently developed ALF and was transferred to the intensive care unit. Over-the-counter drug intake may have been related to heat intolerance and contributed to the event. The patient was successfully treated with conservative measures. In the presence of EHS, it is crucial to act promptly with aggressive total body cooling, in order to prevent progression of the clinical syndrome. Liver function must also be monitored, since it can be a late organ dysfunction.

BACKGROUND

Heat stroke (HS) is a life-threatening condition defined as a severe elevation of the core body temperature (above 40°C) and central nervous system dysfunction.^{1 2} The excessive heat production overwhelms the body's capacity to dissipate heat, usually in a hot and humid environment. This triggers a systemic inflammatory response that can lead to multiorgan dysfunction.³

Classic HS primarily occurs during heat waves and affects elderly or immunocompromised individuals.² It is more frequent than exertional heat stroke (EHS), which is observed in young individuals performing strenuous physical activity in hot environments. Drugs (prescribed or illicit) and genetic conditions are known risk factors.³

This case shows the progression of an EHS to acute liver failure (ALF) that was resolved with conservative measures.

Thus, prompt recognition of this diagnosis is of paramount importance in the appropriate clinical setting. We would also like to draw attention to liver function monitoring, since it can be a late organ dysfunction.⁴

CASE PRESENTATION

In this paper, the authors present the case of a 25-year-old man with a history of hypothyroidism and without any relevant familial history.

The patient reported over-the-counter drug intake in the previous months, namely Provigil (modafinil) and Noopept (n-phenylacetyl-l-prolyl-glycine ethyl ester). Modafinil has been approved

by the European Medicines Agency solely for the treatment of narcolepsy. Its precise mechanism of action has remained elusive. Some pre-clinical models have shown inhibition of dopamine and norepinephrine reuptake. Noopept is an amino acid included in the category of cognitive enhancers.

The patient did not report any recent travels, and had consumed neither herbal supplements nor wild mushrooms. He had a good performance status.

On the day of admission, the patient had been running an outdoor marathon. The weather conditions were mild with temperatures of 17°C and 70% relative humidity. He felt weak and disoriented after running 16 km and was subsequently admitted to the emergency room of a central hospital.

At presentation, the patient's body temperature was elevated (tympanic temperature 39.6°C), with bradypsychia. He was orientated, however, he was not able to repeat words nor could he identify objects. Tachypnoea and tachycardia (150 bpm) were present. Blood pressure was 111/75 mm Hg and the peripheral saturation of oxygen was 98% in room air. The patient was also hypoglycaemic (62 mg/dL; 3.44 mmol/L), and the electrocardiogram showed sinus tachycardia with no further findings.

Therapeutic cooling was undertaken and fluids were administered. The tympanic temperature was below 38°C 6 h after admission.

INVESTIGATIONS

Investigations showed haemoconcentration (haemoglobin 16.6 g/dL; 166.00 g/L), 19 500/μL (19.50×10⁹/L) white cell count, 90.4% (0.90) neutrophils and platelet count 286 000/μL (286×10⁹/L). Biochemistry blood results revealed rhabdomyolysis: creatinine kinase (CK) 483 U/L (8.07 μkat/L; normal 0.67–2.5 μkat/L), myoglobin 4383 μg/L (250.3 nmol/L; normal 1.0–5.3 nmol/L) and an acute kidney injury with creatinine 2.2 mg/dL (194.48 μmol/L; normal 53–106 μmol/L) (Acute Kidney Injury Network (AKIN) 2).

The total bilirubin was mildly elevated (1.92 mg/dL) (32.84 μmol/L; normal 5.0–21.0 μmol/L) and conjugated bilirubin was 1.35 mg/dL (23.09 μmol/L; normal 1.7–5.1 μmol/L), showing mild intrahepatic cholestasis. Alanine aminotransferase (ALT) was below the reference range (36 U/L) (0.60 μkat/L; normal 0.17–0.68 μkat/L). Arterial blood gases showed hyperventilation in room air, without further alterations: pH 7.36, pCO₂ 34 mm Hg

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To cite: Carvalho AS, Rodeia SC, Silvestre J, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214434

(4.52 kPa), pO_2 88 mm Hg (11.70 kPa), $Sa O_2$ 99%, anion gap 12 mmol/L, HCO_3^- 19.2 mmol/L, lactate 1.3 mmol/L.

The patient remained haemodynamically stable and showed neurological improvement during the following 12 h in the emergency department.

Blood tests on the second day revealed that ALT had increased to 10 859 U/L (181.35 μ kat/L) and aspartate aminotransferase (AST) was 11 599 U/L (193.70 μ kat/L; normal 0.17–0.51 μ kat/L). The international normalised ratio (INR) was 5.5 and the total bilirubin level had risen to 4.7 mg/dL (80.39 μ mol/L). Thrombocytopenia (82 000/ μ L platelets) (82×10^9 /L) was detected, along with very low factor V activity (8%) and a low fibrinogen level (1.66 g/L; 4.88 μ mol/L).

The level of ammonia was high (56 μ mol/L) and lactate dehydrogenase reached a maximum of 31 176 U/L (520.64 μ kat/L; normal 1.7–3.4 μ kat/L).

Taken together, these biochemical disturbances reflected ALF.

The patient did not present signs of encephalopathy by then. He was admitted to the intensive care unit (ICU) for further monitoring and possible referral to a liver transplant unit.

DIFFERENTIAL DIAGNOSIS

A diagnostic evaluation for ALF was ordered. Viral and immunological testing all came back negative: acute and chronic hepatitis A, B, C, E; HIV; acute infection with Epstein-Barr virus and cytomegalovirus, general and hepatic-specific auto-antibodies (antinuclear antibodies, extractable nuclear antigen antibodies, anti-liver-kidney microsome antibodies, antimitochondrial antibodies).

The possibility of shock was also taken into account due to potential considerable fluid loss. Nonetheless, despite being tachycardic on admission, the patient revealed neither hypotension nor a significant increase in lactate level throughout admission even during the period of ALF (which could have been associated with a decrease in lactate clearance). As such, this hypothesis was deemed unlikely to justify the patient's clinical condition.

Doppler ultrasonography of the liver vasculature was performed and revealed no evidence of hepatic vein thrombosis, nor of inferior vena cava obstruction nor of any other vascular events.

Thus, the patient was diagnosed with ALF secondary to EHS with signs of severe hepatocellular necrosis.

The influence of the over-the-counter drugs, namely modafinil, was also taken under consideration in the initial diagnostic approach. Although not fully documented, some studies¹ suggest that modafinil can induce a discrete hyperthermic effect during dry heat exposure, under exercise or in resting conditions.² This seems to be related to a lower sweat rate, which can impair heat tolerance and could also have contributed to the event.

TREATMENT

The patient was cooled in the emergency department. Nonetheless, there were no reliable core temperature evaluations (rectal or others) on admission.

Supportive therapy was administrated during the first 3 days—intravenous fluids, including dextrose infusion.

The patient underwent thromboelastogram evaluation and transfusion support was administrated accordingly (fresh frozen plasma and fibrinogen).

A liver transplantation unit was contacted. At the time, the patient did not fulfil the London criteria for emergency

transplantation. Thus, a decision was made to keep him monitored in the ICU.

The patient remained stable with no neurological dysfunction, namely portal-systemic encephalopathy. The aminotransferases reached peak values on the third day and steadily declined thereafter, while the total bilirubin reached the highest value (16.4 mg/dL; 280.51 μ mol/L) on the fifth day (figure 1). The factor V level (figure 2), renal function and rhabdomyolysis parameters returned to normal values during the following days.

OUTCOME AND FOLLOW-UP

The patient was transferred to an internal medicine ward 5 days after ICU admission and discharged 3 days later. On discharge, the patient was clinically stable with normalisation of hepatic and renal laboratory parameters.

DISCUSSION

The case presented describes a healthy, physically fit patient, in whom EHS occurred after strenuous activity performed under moderate heat conditions. The patient had consumed over-the-counter drugs in the previous months.

The temperature measurement in a person who has been performing intense exercise in hot weather conditions must be internally gauged, avoiding the interference of external factors, such as sweat and fluids.¹

It is a known fact that tympanic and axillary measurements are not reliable predictors of core body temperature.^{5 6} This should be taken into account when measuring hyperthermia. In this case, the patient was likely more hyperthermic than what was documented in the emergency department.

Prompt cooling is the cornerstone of treatment and it seems to be the most important prognostic measure.¹ In this particular case, cooling was accomplished in the emergency department after a few hours (according to tympanic measurements), which could also have contributed to the good outcome.

The case also points out the importance of taking the diagnosis of HS into account, particularly when risk factors are present. Known risk factors such as intake of medications that affect heat dissipation (antihistamines, anticholinergics or calcium channel blockers), sleep deprivation and dehydration should be considered.⁷

Multiple organ failure can occur in HS. The mechanism, however, is not yet fully understood and ALF is one of the known complications that should be actively sought. Ischaemia

Figure 1 Evolution of hepatic aminotransferases and bilirubin serum level. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Figure 2 Evolution of factor V serum level.

due to microthrombosis and injury to the vascular endothelium is thought to be implicated in the aetiology.²

Recognition may be delayed when ALF presents mainly with neurological impairment. Causes of ALF must be sought, including hepatitis infection, drug-induced liver injury (including some recreational drugs), severe sepsis, neoplastic infiltration, mushroom ingestion and metabolic diseases.⁸ If the aetiology remains unclear after extensive investigations, liver biopsy should be considered. The condition may progress rapidly when encephalopathy is present and, therefore, patients should be transferred to the ICU and contact with a transplant centre should be made.⁹ Adequate intravascular volume maintenance is recommended on presentation. If hypotension is present, the initial treatment should be intravenous normal saline. There is an increased risk for hypoglycaemia and continuous glucose infusions are adequate in these cases. Nutritional support, including 1.0–1.5 g of enteral protein per kilogram per day, should be carried out due to high energy expenditure in these patients.⁸ Serial evaluation of laboratory coagulation variables is of importance. Most cases have no overt bleeding because of adequate balance between anticoagulant loss and procoagulant factor synthesis.⁸ Usually, the resolution of liver failure is accompanied by resolution of renal dysfunction, when it is present.

Similar cases have been reported in the revised literature. Jin *et al*¹⁰ described the case of a 35-year-old man who was found unconscious after 24 h of physical work under heavy heat load. The diagnosis was EHS and the main finding was ALF and coma. The patient recovered under conservative management (intravenous fluids, cooling, diuretics, such as mannitol and hepatocyte growth-promoting factors). He regained consciousness 7 days after. In this case, the patient fulfilled London criteria for emergency liver transplantation. However, conservative measures were pursued with good results.

Heled *et al*¹¹ also presented four cases of EHS. Cooling measures were initiated immediately in two of them and both recovered completely. The other two cases included one that was misdiagnosed as a conversion disorder, as the patient presented with delirium. Body temperature was not initially measured. The patient was comatose 4 h after and rectal temperature was 39.6°C. Blood tests showed acute renal and liver failure. The patient died within 24 h, despite intensive treatment. The diagnosis of HS was confirmed on autopsy. The other case was that of a 20-year-old soldier who collapsed

while running. He had a rectal temperature of 40.5°C. Cooling measures were only initiated 2 h after and 2 g of paracetamol were given. The patient's condition deteriorated with ALF, disseminated intravascular coagulation and acute respiratory distress syndrome. Preparation for liver transplantation was initiated. However, the patient died with multiple organ failure on the fifth day. The diagnosis of HS was also confirmed post-mortem.

These cases and other studies have shown that, if temperature is reduced to less than 40.0°C within 30 min after the loss of consciousness, the mortality rate is negligible.¹ Some authors refer to this time frame as 'the golden half-hour in the realm of EHS'.¹

Antipyretics have no proven role in HS management. Antipyretics interrupt the change in the hypothalamic set point caused by pyrogens.¹² The opposite happens in HS, where a healthy hypothalamus is overloaded, so antipyretics are not expected to work. Moreover, antipyretic use can be harmful in the case of patients who develop hepatic, haematological or renal complications.

Prophylactic transfusion of plasma is not recommended. In the absence of haemorrhage, this procedure conceals trends in the INR, which is an important marker of prognosis.⁸ It can also cause volume overload or transfusion-related acute lung injury.

Presently, there are no established definite indications for liver transplantation in HS. Some studies showed that conservative management was successful in cases of EHS.¹⁰ Patients with non-paracetamol ALF with progressive coagulopathy should be discussed with a transplant centre. King's College Hospital criteria can help to guide management.¹³

Heat waves are associated with marked short-term increases in mortality and the consequences are usually more disastrous in Southern Europe. A heat wave is defined by temperatures higher than expected for a given time of year. High levels of humidity often accompany such weather conditions. To date, no standard definition has been formulated. Different temperatures and a variable number of days have been considered throughout the literature.¹⁴

In Portugal, the definition of heat wave considers a rise of the daily mean temperature by a fixed absolute amount (5°C), during at least six consecutive days.¹⁵ There were four heat waves in this country during the past few decades (1981, 1991, 2003 and 2013). In 2013, 1684 heat-related deaths were reported. The most common cause is classical HS.

Climate changes, an ageing population and some medications could mean that the number of heat-related disorders might rise in the coming years.

Patient's perspective

- "I do a lot of sports and would consider myself as very fit. In the past, I had already participated in three different half marathons, all of them under more or less similar conditions. One of the main differences to this one was the lack of training. Normally, I had trained at least 4–8 weeks. During the 4 months before the incident I trained only twice. On the day of the run after around 7–10 km I felt that this day was not going to be my best running day. I felt like I was not getting into any rhythm while running. I kept

drinking (water and Powerade, which was offered on the track) and tried to keep up the speed. Recalling this now I think one major mistake was not to run at "my own speed" but instead forcing myself to run faster in order to achieve a special time. I felt that the heat was rising. I remember that I perceived the sun to be very hot and was sweating a lot. I cannot recall it for sure but at kilometre 14 I already felt dizzy and had begun to feel goose bumps on my neck. I almost felt a bit cold. I could not think straight or rationally any more and stopped drinking. I remember that I wanted to finish the run and not stop or begin to walk. My legs and especially my calves were hurting and I was already running quite slow but did not want to stop. Then suddenly everything became white and I sat down and fainted.

- ▶ When I woke up in the emergency tent near the running track I had no memory of the marathon and the beginning of the day. It seemed like I woke up from a dream that I could not remember. Everything was blurry and I was beginning to wonder how I got there. I knew that I was in the city and for which purpose but could not recall what happened. I was shaking and felt very weak and feverish. In addition, I could not control my hands and arms like I wanted to. The most difficult and concerning fact was that I could not talk properly. I had the impression that I remembered all the words but still I was not able to pronounce them. Therefore communication with the doctors in the tent and later in the hospital was quite difficult. Arriving in the hospital I became clearer. Still, I could not speak properly or remember anything; but the shaking stopped. Once in the emergency section, it helped a lot to talk with a young doctor who helped me communicate by asking a lot of questions I was able to answer positively or negatively. Once he told me what happened I could recall the event very briefly in my mind. I still had cramps in my hands and legs, and could not control them like I wanted to and felt sick.
- ▶ The next days in the hospital are a bit blurry for me now. From today's perspective, they seemed to pass by quickly. I remember that I could talk again at the end of the day but that I had strong diarrhoea and could not keep food or drinks in my body very well. I had strong appetite for especially sweet drinks but was not supposed to have them. My legs were continuously hurting like a muscle ache after too much training only stronger. Sometimes it even felt like parts of the muscles were destroyed. When I was transferred to the intensive care unit I felt better in terms of the cramps and the fever but had absolutely no appetite. The first days I wanted to vomit almost after every food consumption and did not want to eat much. Concerning the liver and kidney failure I cannot recall a special feeling connected to it. There was no concrete pain but a steady weakness and lack of appetite.
- ▶ Throughout the whole process the doctors and additional employees from the hospital were extremely generous and helpful, and strongly supported me in the recovering process."

Learning points

- ▶ Core temperatures higher than 39–40°C degrees should raise the suspicion of non-infectious causes. Tympanic or axillary measurements are not reliable predictors of central body temperature.
- ▶ Heat stroke (HS) is manageable. It is crucial to recognise and act promptly with cooling measures to prevent the progression of a clinical syndrome. Risk factors such as drugs should be actively sought.
- ▶ Antipyretics have no role in HS management and can be harmful.
- ▶ Acute liver failure (ALF) may be of late onset. Early discussion with a liver transplantation centre may be crucial to guide management.
- ▶ A higher number of cases of HS are expected in the future, since the population is ageing and more heat waves are also anticipated, due to climate changes.

Contributors ASVDC, JS and PP were the main physicians in charge of the patient while in the intensive care unit. SCR was the main physician caring for the patient in the emergency department. ASVDC and SCR performed the literature review. ASVDC wrote the draft. SCR, JS and PP reviewed and agreed on the draft.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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