36-Year-Old Man With Respiratory Distress and Altered Mental Status

Pierpaolo Turcano, MD, and Razvan M. Chirila, MD

A 36-year-old man with no remarkable medical history presented to the emergency department with respiratory distress and altered mental status after several hours of intense aerobic exercise in hot and humid weather. The patient lost consciousness and fell backward from a sitting position, resulting in head trauma. No obvious shaking or jerking movements were observed. The fall was witnessed by military personnel who responded quickly by pouring cold water on him and calling emergency medical services; the patient was actively enrolled in physical training at a Florida Navy facility at the time of presentation. On arrival at the emergency department, the patient was quickly intubated, and resuscitative measures were initiated; he was transferred to the intensive care unit for further management.

On physical examination, obtundation was noted, and the patient's Glasgow Coma Scale (GCS) score (range, 3 to 15) was 3. His temperature was as high as 40.6°C, and he was tachycardic, with a heart rate of 140 beats/min and regular rhythm, blood pressure of 84/51 mm Hg, respiratory rate of 37 breaths/min, and oxygen saturation of 83% while the patient breathed room air. He appeared to be mildly distressed. On eye examination, his pupils were round, equal in size, and reactive to light, with intact extraocular movements. Pulmonary examination revealed no wheezing, rales, or rhonchi. Findings on cardiac and abdominal examinations were normal with the exception of tachycardia. A neurologic examination was limited by the patient's altered mental status; however, muscle tone was normal and reflexes were intact bilaterally.

Laboratory studies yielded the following (reference ranges provided parenthetically): white blood cell count, 9.4 × 10^9/L (3.6 to 9.6 × 10^9/L) with normal differential; hemoglobin, 17.3 g/dL (13.2 to 16.6 g/dL); hematocrit, 50.1% (38.3% to 48.6%); platelet count, 110 × 10^9/L (135 to 317 × 10^9/L); sodium, 144 mmol/L (135 to 145 mmol/L); potassium, 2.6 mmol/L (3.6 to 5.2 mmol/L); chloride, 108 mmol/L (98 to 107 mmol/L); bicarbonate, 18 mmol/L (22 to 29 mmol/L); calcium, 8.5 mg/dL (8.6 to 10.0 mg/dL); phosphorus, 1.0 mg/dL (2.5 to 4.5 mg/dL); creatinine, 2.4 mg/dL (0.74 to 1.35 mg/dL); lactate, 7.7 mmol/L (0.5 to 2.2 mmol/L); lactate dehydrogenase, 630 U/L (122 to 222 U/L); creatine kinase, 20,820 U/L (26 to 192 U/L); total bilirubin, 0.8 mg/dL (≤1.2 mg/dL); and thyrotropin, 3.96 mIU/L (0.3 to 4.2 mIU/L). Urine screening was negative for drugs of abuse. Urinalysis revealed 7 hyaline casts per high-power field (hpf), 1 to 3 granular casts per high-power field, 1 to 3 red blood cell casts per hpf, calcium oxalate crystals, and no other abnormalities.

1. **Which *one* of the following *most likely* accounts for the patient's initial clinical manifestations?**
   a. Serotonin syndrome
   b. Malignant hyperthermia
   c. Exertional heat stroke (HS)
   d. Heat exhaustion
   e. Neuroleptic malignant syndrome

Serotonin syndrome is associated with increased serotoninergic activity in the central nervous system (CNS), often due to interactions between drugs (eg, selective serotonin reuptake inhibitors) or intentional self-poisoning. Serotonin syndrome is a clinical diagnosis, and patients may often present with delirium and restlessness. Hyperthermia

See end of article for correct answers to questions.

Resident in Neurology, Mayo Clinic School of Graduate Medical Education, Jacksonville, FL (P.T.); Advisor to resident and Consultant in General Internal Medicine, Mayo Clinic, Jacksonville, FL (R.M.C.).

is common, as well as tachycardia and hypertension. Neuromuscular hyperactivity can manifest as tremor, muscle rigidity, myoclonus, and hyperreflexia.[1] Malignant hyperthermia is an autosomal dominant condition occurring in susceptible patients exposed to a volatile anesthetic (eg halothane) or succinylcholine.[2] The onset is typically within 1 hour after the administration of anesthesia, and generalized muscle rigidity, hyperthermia, and cardiac arrhythmias are the most common features. Laboratory studies often reveal hyperkalemia, elevated creatine kinase level, and myoglobinuria.

Exertional HS is a medical emergency defined as a core body temperature elevated above 40.6°C with CNS depression and arrhythmias that may quickly lead to multiorgan failure and death.[3]

Heat exhaustion is defined as a core body temperature between 38.3°C and 40.0°C (101°F to 104°F) without CNS involvement.[4] Neuroleptic malignant syndrome is an idiosyncratic reaction most often seen with the use of antipsychotic medications. Patients often present with altered mental status, high temperature, tachycardia, tachypnea, and generalized hypertonia. Elevated serum levels of creatine kinase as well as lactate dehydrogenase, alkaline phosphatase, and liver enzymes are common. Rhabdomyolysis leading to acute kidney injury can develop if not treated.[5]

Our patient presented with multiple systemic manifestations including neurologic, cardiovascular, and renal abnormalities. Althoughmany of the clinical findings observed are not specific and can be associated with several other disorders, the clinical picture, along with the anamnestic details, were most consistent with a diagnosis of HS.

With a presumptive diagnosis of exertional HS, supportive therapy was started with fluids; cardiac function was monitored with continuous telemetry. The patient was intubated for airway protection, and cooling measures were initiated.

2. **Which *one* of the following is the *most important* initial management for this patient's condition after airway, breathing, and circulation are secured?**
   a. Cooling core body temperature with goal of less than 37.0°C
   b. Cooling core body temperature with goal of less than 38.9°C
   c. Immediate oral hydration
   d. Rest until recovery
   e. Monitoring body temperature with oral thermometers

Transporting the patient to the nearest hospital while supporting organ system function and assessing airway, breathing, and circulation should take place immediately, followed by quick reduction of the core body temperature. A rapid cooling of the patient's body temperature below 37.0°C is not recommended, and it may cause cardiac arrhythmias. Cooling measures with a goal of less than 38.9°C should be started in situ and continued during transportation to the hospital.[6]

Although fluid resuscitation should be started as soon as possible, intravenous fluids are preferred over oral rehydration because of a more rapid effect in reversing hypovolemic status, especially in the setting of underlying neurologic deficits, as commonly seen in patients with HS. Heat stroke is a medical emergency, and treatment should be started as soon as possible. Resting until recovery is not advised because potential life-threatening complications may develop quickly. The patient's temperature should be monitored constantly, preferably with a rectal thermistor probe calibrated for high temperatures. Rectal temperature is typically higher than oral, and a rectal probe allows for constant monitoring as cooling is taking place.

Our patient was transported by emergency medical services and arrived at the emergency department roughly 1 hour after symptom onset; inotropic support and fluid resuscitation were administered to manage profound hypotension, and continuous renal replacement therapy was initiated because of the patient's worsening renal function. Cooling measures were started.

3. **Which *one* of the following is the *most effective* method to reduce the core body temperature in this patient's condition?**

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a. Ice water (between 2.0°C and 10.0°C) immersion
b. Ice packs over major arteries
c. Dantrolene
d. Fanning (evaporating and convective cooling)
e. Antipyretic medications

Ice water immersion has been proved effective for both exertional and nonexertional HS, with cooling rates of 0.15°C/min to 0.22°C/min. This treatment has led to lower rates of morbidity and mortality when compared with other therapeutic options. Shivering and agitation may occur as a result of the treatment. Theoretically, intravascular cooling devices could be used and have produced overall good outcomes. However, only scattered case reports have been published, and there are no clinical trials to prove their superiority over external cooling systems.

Application of ice packs or crushed ice on the body to lower the body temperature has limited application because of the lack of definitive rates of cooling as well as suboptimal outcomes.

Dantrolene has been studied as a possible therapeutic agent for HS given its use in other heat-related disorders such as malignant hyperthermia. However, no difference in rates or outcomes has been observed, and its use is not recommended in clinical practice.

Fanning consists of directing air at the patient while simultaneously spraying the body with water. Higher morbidity and mortality rates have been observed with this technique, likely due to the studied population being older. In an effort to prevent shivering, a device called a *body-cooling unit* sprays a combination of cold water at 15°C and warm water at 45°C with air to achieve a surface skin temperature of 32°C to 33°C. Although the body-cooling unit has proved efficacy, its superiority compared with ice water immersion has not been documented. Overall, cold water immersion is the most effective strategy for the rapid treatment of HS.

No pharmacological agent has been documented to be helpful in the treatment of HS. However, an increase in heat stress–induced cytokines in patients with HS has led some investigators to believe that antipyretic drugs might be used as a treatment option. Because these medications have only been given concomitantly with other cooling techniques, no assumption on their efficacy can be made without further studies.

In our patient, the Arctic Sun Temperature Management System (Becton, Dickinson and Company) was utilized. This system operates under negative pressure and circulates cool water through hydrogel applied over the abdomen, back, and thighs. Fanning and ice packs over the forehead, axilla, and groin were also applied. The patient's initial temperature of 40.6°C was brought down to 39°C within 30 minutes of arrival. His temperature returned to a normal core body temperature approximately 3 hours later.

Later that day, purpura developed on the patient's left forearm. A laboratory panel revealed a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), as well as an elevated international normalized ratio (INR), hypofibrinogenemia, thrombocytopenia, and an increased D-dimer level.

4. **Which *one* of the following complications *best* explains this patient's abnormal clinical and laboratory findings and purpura secondary to HS?**
   a. Disseminated intravascular coagulation
   b. Hemolytic uremic syndrome
   c. Heparin-induced thrombocytopenia
   d. Rhabdomyolysis
   e. Thrombotic thrombocytopenic purpura

Disseminated intravascular coagulation is characterized by widespread activation of coagulation mediated by exaggerated proinflammatory cytokine production, which results in thrombotic occlusion of small and midsize vessels. It is usually an acquired disorder, most likely secondary to severe sepsis, trauma, obstetric complications, and malignancy among many other causes. A progressively decreasing platelet count and

fibrinogen level as well as prolonged PT/INR and aPTT and increased D-dimer concentrations are frequently observed.[7] Hemolytic uremic syndrome refers to a triad of hemolytic anemia with red blood cell fragments, thrombocytopenia, and acute kidney injury, usually occurring after a prodromal gastrointestinal illness related to Shiga toxin–producing strains of *Escherichia coli*. Patients' PT/INR, aPTT, and fibrinogen levels are usually normal in this disorder.

Heparin-induced thrombocytopenia is a rare drug-induced autoimmune disorder caused by the formation of autoantibodies that cause platelet activation through the formation of complexes of heparin and platelet factor 4. Thrombocytopenia usually develops 5 to 8 days after patients start receiving heparin treatment. Although the platelet count is low, PT/INR, aPTT, and fibrinogen levels are usually normal.

Rhabdomyolysis is a clinical entity characterized by muscle destruction and subsequent release of intracellular enzymatic contact into the bloodstream, leading to organ damage. It is usually associated with dark urine, marked elevation of serum creatine kinase level, acute kidney injury, and normal results on coagulation studies.[8]

Thrombotic thrombocytopenic purpura is defined as a severe deficiency of the protease ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13), leading to an accumulation of large von Willebrand factor multimers in the vasculature; these multimers precipitate the formation of platelet-rich thrombi, leading to thrombocytopenia and increased risk of bleeding; PT/INR, aPTT, and fibrinogen levels are usually normal in this condition.

Based on the clinical picture and laboratory findings, disseminated intravascular coagulation was diagnosed. The treatment is focused on treating the underlying condition and preventing further organ failure. The patient was aggressively treated with supportive measures including fluids and vasopressors. Careful clinical and laboratory monitoring of fibrinogen level, platelet count, hemoglobin level, and coagulation profile was performed; platelet transfusion was necessary in this patient.

The patient continued undergoing intermittent hemodialysis; he slowly improved over the following week, with resolution of his symptoms and improvement of his clinical picture.

5. **Which *one* of the following statements is *true* regarding this patient's prognosis?**
   a. In-hospital mortality is around 70%
   b. Promptly decreasing the body temperature below 37°C within 30 minutes of presentation improves survival
   c. Previous treatment with diuretics is not associated with a worse prognosis
   d. Cardiovascular failure at admission does not modify HS risk of mortality
   e. Residual brain damage is a possible complication (up to 20%)

The risk of in-hospital mortality associated with HS is around 20% if HS is promptly and adequately treated, and most patients fully recover after the acute phase. Decreasing the body temperature below 37°C within 30 minutes of presentation could cause additional complications such as cardiac arrhythmias. Trials have found improved survival rates when the body temperature is decreased below 38.9°C within 30 minutes of presentation. Negative prognostic factors associated with HS include previous use of diuretics, age older than 80 years, hypotension at presentation, GCS score of less than 12, and a history of cancer. An increased troponin level at presentation and cardiovascular failure are associated with a worse prognosis and increased risk of mortality. All patients have varying degrees of CNS dysfunction at the time of HS diagnosis, with 20% resulting in residual brain damage, likely due to anoxic injury, cerebral ischemia, or electrolyte imbalance.

Our patient had a GCS score of 3 at presentation and electroencephalographic evidence of severe, nonspecific encephalopathy. Repeated electroencephalography performed later during hospitalization revealed improved brain electrical activity, and the patient returned to his

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baseline mental status with a GSC score of 15. Prior to discharge, the patient was completely weaned from the ventilator and pressor support; his cardiac ejection fraction improved from an initial level of 42% to 66%. Disseminated intravascular coagulation resolved, his renal function improved significantly, and he was able to discontinue hemodialysis therapy within 1 month after discharge.

DISCUSSION

Hyperthermia occurs along a continuum starting with heat stress, moving through heat exhaustion, and ending with HS. Clinically, HS is a medical emergency defined as a core body temperature above 40.6°C (105°F), at which point multiorgan failure can occur if HS is not promptly treated.[6] Heat stroke can be further classified into exertional, usually occurring in previously healthy young individuals who exercise in hot humid climate conditions, and nonexertional (or classic), which occurs during heat waves and poses increased risk to the elderly population. Heat stroke is often underreported or misdiagnosed, and its reported incidence ranges from 17.6 to 26.5 cases per 100.000 persons.[9] Our limited understanding of the pathophysiology underlying HS reflects the inability to predict, diagnose, and promptly treat this condition. Sleep deprivation,[10] extreme age (younger than 15 or older than 65 years), exposure to hot and humid environments, and genetic susceptibility have been associated with HS onset.[11,12]

Patients present with extremely high core body temperature in association with CNS dysfunction[6]; however, any organ can potentially be involved. Neurologic findings may range from weakness, confusion, inappropriate behavior, and impaired judgment to delirium, seizures, and even coma and death. These findings are common in both exertional and classic HS, but they seem to be more transient in the former. Hypoxic ischemic damage, especially in the cerebellum, has often been described in patients with HS, leading to progressive cerebellar atrophy. Magnetic resonance imaging may also reveal increased signal in diffusion sequences as a result of possible myelinolysis-related cellular damage. Some investigators believe that the neurologic damage is secondary to hypernatremia; regardless of the underlying pathophysiologic mechanism, up to 20% of HS cases may have long-term consequences such as parkinsonism and ataxia.[11]

Cardiac manifestations include tachyarrhythmias (atrial fibrillation, supraventricular tachycardia, and sinus tachycardia), QT prolongation, and conduction defects (most commonly right bundle branch block). Myocardial infarction may occur as a possible complication.

Laboratory evaluation usually reveals hemoconcentration, elevated serum urea nitrogen and creatinine levels from renal damage, increased hepatic enzymes, and electrolyte abnormalities.

No single diagnostic test definitely confirms or excludes HS, making history and physical examination extremely important in this condition. Frequently, patients with HS meet criteria for systemic inflammatory response syndrome. In patients whose mental status does not respond to cooling treatment, alternative causes for hyperthermia should be investigated, including hypothalamic infarct, meningitis, encephalitis, and cerebral hemorrhage. A number of medications can interfere with thermal regulation and can mimic HS, such as anticholinergic agents, barbiturates, propofol, and sympathomimetics (including cocaine, amphetamines, ephedrine, and dietary supplements containing ephedra).

The cytotoxic effect of heat is a function of the degree and duration of hyperthermia, and thus, early recognition of HS should be followed by immediate cooling of the body and organ system function support. Rapid cooling to a body temperature below 38.9°C within 30 minutes of presentation has been reported to improve survival. It can be achieved by conductive cooling technique via ice water immersion of the patient, but shivering may occur during the treatment, preventing the cooling process. Evaporating and convective cooling techniques involving directing air to the body surface while simultaneously

spraying water on the patient, along with appropriate pharmacological treatment including the use of benzodiazepines or narcotics may prevent the patient from shivering. Additionally, interventions to support the airway, breathing, and blood pressure may be necessary, as well as ways to prevent end-organ damage. The optimal target temperature at which the cooling should end is between 38.0°C and 38.9°C. No pharmacological agent has proved efficacy in lowering the core body temperature of these patients. Mortality rates can be as high as 30% in the elderly population. The presence at admission of anuria, cardiovascular failure, increased PT, and a higher body temperature have been associated with an increased risk of mortality.Additionally, 20% of patients who survive the acute phase have varying degrees of neurologic dysfunction and severe disability at discharge.[11]

Classic and exertional HS are rare but increasingly emerging life-threatening disorders with significant morbidity and mortality; recent studies have predicted that the incidence of heat stroke and heat-related disorders may increase in the future, not only because these conditions may be better recognized by physicians but also because of the increase in global warming, which may in turn lead to an increased frequency and incidence of heat waves.[6] Ongoing research is aimed at preventing new cases by limiting the risk factors as well as defining the best therapeutic options. Special care must be taken for those at increased risk such as the elderly population living in extremely hot and humid environments. The prognosis depends on a time-effective response and treatment; further studies are needed to unmask the underlying molecular mechanisms and design an appropriate therapeutic agent.

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Correspondence: Address to Razvan M. Chirila, MD, Division of General Internal Medicine, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224 (razvan.chirila@mayo.edu).

ORCID

Pierpaolo Turcano: https://orcid.org/0000-0002-3240-8348

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Correct Answers: 1. c. 2. b. 3. a. 4. a. 5. e