Successful treatment with hydrocortisone for heat stroke with critical illness-related corticosteroid insufficiency: transitional changes in serum cytokine and cortisol concentrations

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Abstract
A 37-year-old man was transferred to our emergency center because of heat stroke with circulatory shock. Despite aggressive body cooling, massive intravenous transfusion, and supply of inotropic agents, shock was persistent. To evaluate adrenal function, an adrenocorticotropic hormone stimulation test was conducted and the results indicated that he had critical illness-related corticosteroid insufficiency (CIRCI) as a result of adrenal insufficiency. Continuous hydrocortisone administration was started and he recovered from shock within a few hours. He was discharged on the thirty-seventh hospital day. Serum cortisol and cytokine concentrations were initially high and the cytokines decreased subsequent to hydrocortisone administration. It is speculated that CIRCI is an exacerbating factor in heat stroke, and hydrocortisone may be a potential therapeutic approach in such patients.

Key words Heat stroke · Adrenocorticotropic hormone · Cortisol · Cytokine

Introduction
Recently, air temperature around the world has been rising because of global warming. Since the 1990s, many people have suffered from heat stroke during severe heat waves in the United States and Europe, in 1995 and 2003, respectively [1,2]. We collected the data from all cases of heat illness for 1 year in our prefecture and reported the results in 2007 [3]. The tendency in Japan has also been the same.

Heat illness is caused by exposure to a hot environment or by excessive exertion. Heat stroke is defined as the most severe form of heat illness and is characterized by a high body temperature, of more than 40° Celsius and by central nervous system dysfunction, such as delirium, convulsions, and coma [4]. It can be a fatal illness, and its incidence will increase in the near future.

We report a patient with heat stroke with circulatory shock. He was treated with hydrocortisone and had a good outcome. We measured his serum cortisol and cytokine concentrations and in this report we discuss the therapeutic efficacy of hydrocortisone in heat stroke.

Case report
A 37-year-old man suffered a consciousness disturbance while working in scorching heat in August. The maximum air temperature was 34.8° Celsius and humidity was 51%. His colleagues moved him to a shaded area and cooled down his body with water; however, his consciousness disturbance was not alleviated. He was transported to a hospital by ambulance 1 h after the onset. When he arrived there, his Glasgow Coma Scale (GCS) level was 3 (E1V1M1). His blood pressure, heart rate, and respiratory rate were 118/79 mmHg, 142 bpm, and 28 breaths·min⁻¹, respectively. His body temperature (axillary) was 41.8° Celsius. Immediately, body cooling and massive fluid transfusion were started. But his blood pressure gradually decreased and a blood gas analysis showed hypercapnea and metabolic acidosis (fractional inspired oxygen [FIO₂], 1.0; pH, 7.14; P aO₂, 91.5 mmHg; P aCO₂, 56.7 mmHg; base excess [BE], −9.2 mmol·l⁻¹; HCO₃⁻, 15.9 mmol·l⁻¹). After tracheal intubation, he was transferred to our medical emergency center.

On admission, his GCS, blood pressure, heart rate, respiratory rate, and body temperature (bladder) were: 3 (E1V1M1), 110/40 mmHg, 140 bpm, 24 breaths·min⁻¹, and 39.8° Celsius, respectively. On head computed tomography (CT), there was no significant finding which
indicated any cause of the consciousness disturbance. From the physiological findings and laboratory data, he was diagnosed as having heat stroke associated with respiratory failure, disseminated intravascular coagulopathy, and acute renal failure. The amount of crystalloid transfusion reached 20,000 ml during the first 24 h after admission. Mechanical ventilation (F\textsubscript{O\textsubscript{2}}, 1.0; positive end-expiratory pressure [PEEP], 8 cmH\textsubscript{2}O) and continuous hemodiafiltration were performed. His core body temperature (bladder) cooled down to 36° Celsius within 8 h after the onset. Despite massive intravenous transfusion and inotropic agents such as dopamine, dobutamine, and norepinephrine, he was in persistent circulatory shock (blood pressure decreased to 50/30 mmHg and heart rate increased to 150 bpm). The circulatory parameters, measured with a pulmonary artery catheter (Swan-Ganz CCOMbo Pulmonary Artery Catheter; Edwards Lifescience, Irvine, CA, USA), showed decreased somatic vascular resistance of 800–1100 dyne·s·cm\textsuperscript{-5}·m\textsuperscript{2} and an increased cardiac index of 6.5 l·min\textsuperscript{-1}·m\textsuperscript{2}. In order to search for a site of infection, we repeatedly checked cultures of blood, sputum, and urine, and X-ray and CT scans, but there were no data indicating the existence of any infections during the clinical course.

We conducted an adrenocorticotropic hormone (ACTH; tetracosactide acetate) stimulation test to evaluate adrenal function on his third day in the intensive care unit (ICU). Synthetic ACTH 0.25 mg was intravenously injected. Serum cortisol concentrations were measured before and 30 and 60 min after the ACTH injection (Table 1). He was diagnosed as having critical illness-related corticosteroid insufficiency (CIRCI) as a result of adrenal insufficiency, which has been defined in previous reports as the condition of a less than 9 μg·dl\textsuperscript{-1} maximum increment of serum cortisol concentration after ACTH injection [5,6]. After this diagnosis, continuous hydrocortisone infusion of 200 mg·day\textsuperscript{-1} was started, from the third ICU day. A few hours after the first injection, his blood pressure gradually increased (Fig. 1). Consequently, he recovered from circulatory shock and the inotropic agents could be tapered off on the fifth ICU day. Hydrocortisone administration of 200 mg·day\textsuperscript{-1} was continued for 7 days. The dose was reduced to 100 mg·day\textsuperscript{-1} on the tenth ICU day, and reduced to 50 mg·day\textsuperscript{-1} on ICU day 11, and then discontinued on ICU day 12. When the hydrocortisone administration was stopped, his general condition, including circulation and respiration, was still stable and we found no adverse effects of the hydrocortisone therapy. Mechanical ventilation was discontinued on ICU day 15. Reevaluation of adrenal function by the ACTH stimulation test on ICU day 28 showed a normal response (Table 1). There were no serious complications except for speech and gait disorders that were caused by central nervous injury caused by high core temperature. He was discharged from our hospital on hospital day 37.

After obtaining informed consent from his wife, we had obtained arterial blood samples on ICU days 2, 3, 4, and 8. These samples were separately injected into sterile tubes. After being left for at least 30 min at 4° Celsius, the tubes were centrifuged at 3000 rpm for 10 min. The supernatant liquid (serum) was aspirated and separately injected into sterile tubes and these tubes were frozen at −80° Celsius for preservation. Serum cortisol concentrations were measured by an enzyme-linked immunosorbent assay (ELISA; Cortisol ELISA; IBL, Hamburg, Germany). Serum cytokines were analyzed by the Bio-Plex Cytokine Human 8-Plex panel (Bio-Rad Laboratories, Hercules, CA, USA). The transitional changes in serum cortisol and cytokine levels in the early phase are shown in Fig. 2.

### Table 1. ACTH stimulation test in the patient

<table>
<thead>
<tr>
<th></th>
<th>Before ACTH</th>
<th>After 30 min</th>
<th>After 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU day 3 (μg·dl\textsuperscript{-1})</td>
<td>32.1</td>
<td>37.0</td>
<td>37.9</td>
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<tr>
<td>ICU day 28 (μg·dl\textsuperscript{-1})</td>
<td>15.7</td>
<td>50.7</td>
<td>40.7</td>
</tr>
<tr>
<td>Normal range (μg·dl\textsuperscript{-1})</td>
<td>(4.0–18.3)</td>
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ACTH, adrenocorticotropic hormone; ICU, intensive care unit

### Discussion

Heat stroke is a life-threatening illness characterized by an excessive elevation of body temperature with central nervous system disturbance. Exposure to a hot environment and disorder of thermoregulatory function generate heat stroke. In order to prevent organ failure, effective core body cooling in the early phase is essential [4]. However, once heat stroke develops, cooling is not enough to alleviate the pathophysiological manifestations of the thermoregulatory function disorder.

The main pathophysiology of heat stroke is endothelial injury caused by heat exposure. Endothelial injury induces the release of inflammatory cytokines, and the cytokine cascade causes further endothelial injury, vascular dilatation, and organ dysfunction, which is a similar condition to sepsis. Excessive stress and inflam-