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RAPID COMMUNICATION

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Heat stroke leading to acute liver injury & failure: A case series from the Acute Liver Failure Study Group

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Abstract

Background & Aims: In the United States, nearly 1000 annual cases of heat stroke are reported but the frequency and outcome of severe liver injury in such patients is not well described. The aim of this study was to describe cases of acute liver injury (ALI) or failure (ALF) caused by heat stroke in a large ALF registry.

Methods: Amongst 2675 consecutive subjects enrolled in a prospective observational cohort of patients with ALI or ALF between January 1998 and April 2015, there were eight subjects with heat stroke.

Results: Five patients had ALF and three had ALI. Seven patients developed acute kidney injury, all eight had lactic acidosis and rhabdomyolysis. Six patients underwent cooling treatments, three received *N*-acetyl cysteine (NAC), three required mechanical ventilation, three required renal replacement therapy, two received vasopressors, one underwent liver transplantation, and two patients died—both within 48 hours of presentation. All cases occurred between May and August, mainly in healthy young men because of excessive exertion.

Conclusions: Management of ALI and ALF secondary to heat stroke should focus on cooling protocols and supportive care, with consideration of liver transplantation in refractory patients.

KEYWORDS
acute liver failure, heat stroke, liver transplantation, multi-organ system failure, rhabdomyolysis

1 | INTRODUCTION

There were an estimated 7233 heat-related deaths in the United States from 1999 to 2009.[1] The most serious heat-related illness is heat stroke,[2] defined as having elevated body temperature ≥40°C with central nervous system dysfunction, and is divided into classical and exertional subtypes. Classical, or non-exertional, heat stroke (CHS) is more common in elderly and immunocompromised individuals and

Abbreviations: AKI, acute kidney injury; ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; ALI, acute liver injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHS, classical heat stroke; ED, emergency department; EHS, exertional heat stroke; HE, hepatic encephalopathy; HVP, high volume plasma exchange; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; LT, liver transplantation; NAC, *N*-acetyl-cysteine; RRT, renal replacement therapy; sCR, serum creatinine; TFS, transplant free survival.

associated with elevated environmental temperatures such as in heat waves. Exertional heat stroke (EHS) occurs in younger individuals associated with vigorous activities such as marathons.[3,4] Over the next century, the frequency and intensity of heat waves will likely increase because of climate change.[5] Heat stroke should be preventable and early diagnosis and treatment could reduce morbidity and mortality.

Hepatocellular injury is a well-documented complication of heat stroke,[6] but few case reports[7-9] have described an association with acute liver injury or failure (ALI/ALF). Treatment of ALF from heat stroke involves mainly supportive care;[8] few centres have performed liver transplantation (LT).[10,11] We describe the clinical characteristics and outcomes of ALI and ALF caused by heat stroke in a large North American prospective ALI/ALF cohort.

Key points

- Heat stroke is a rare cause of acute liver injury and failure.
- Majority of patients were young, previously healthy males and developed exertional heat stroke.
- Clinical features included acute kidney injury, lactic acidosis, thrombocytopaenia and rhabdomyolysis.
- Supportive care with cooling protocols led to transplant free survival in five of eight patients.

2 | METHODS

Between January 1998 and April 2015, 2675 adult patients with ALI or ALF of all etiologies were enrolled in the Acute Liver Failure Study Group (ALFSG) registry from a total of 31 academic medical centres in North America. All patients enrolled met entry criteria for ALF, defined as coagulopathy (INR ≥ 1.5), and any grade of hepatic encephalopathy (HE defined clinically by the West Haven criteria[12]), within 26 weeks of the first symptoms and in the absence of pre-existing chronic liver disease.[13] A second category of patients were classified as acute liver injury (ALI), which has been defined by the ALFSG as patients with an INR ≥ 2.0 in the absence of pre-existing liver disease and no encephalopathy. The overall study design and human research concerns were reviewed every 6 months by a Data and Safety Monitoring Board appointed by the National Institute of Digestive and Kidney Diseases (NIDDK). In addition, each centre's Institutional Review Board approved the study on an annual basis. Informed consent was obtained directly from ALI patients. In cases meeting criteria for ALF, consent was obtained from each patient's next of kin or health proxy, since by definition patients were unable to consent because of encephalopathy, and consent was revisited with the patient following recovery of mental functioning (Forms S1 and S2). Clinical data and bio-samples were collected from each study subject for 7 days with follow up visits at 6 months and 1 year. The ALF etiology was determined by the site investigator and later reviewed by a central causality committee for confirmation. Eight cases were classified by the site investigator as "Other: heat stroke" and subsequently confirmed by temperature ≥40°C and clinical data to rule out other causes. If the patient's encephalopathy resolved after resuscitation for heat stroke and the INR was ≥2.0, the patient was diagnosed with ALI. If the encephalopathy persisted after resuscitation for heat stroke, the patient was diagnosed with ALF.

Each site utilized its own criteria for liver transplantation but in general followed AASLD guidelines and the United Network Organ Sharing (UNOS) Status 1 criteria: age ≥18 years, life expectancy <7 days without liver transplantation, residence in an intensive care unit (ICU), no pre-existing liver disease, and either ventilator dependence, renal replacement therapy, or INR > 2.0.[13,14] Descriptive analysis was used to compare patient demographics, medical history, clinical characteristics and outcomes (transplant-free survival [TFS], LT, death). We also compared ALI/ALF heat stroke patients to acetaminophen (APAP) and ischaemia aetiologies of ALI/ALF. Medians were reported with interquartile ranges (IQR) and compared with the Wilcoxon rank-sum test. Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Clinical presentation

Five of the eight patients had ALF and three had ALI. There were seven patients with EHS and one with CHS. Four EHS cases were associated with long distance running, one was associated with treadmill use while wearing a sweat suit and wrapped in plastic, one was associated with military drills, and one was found unconscious in a field. The CHS case occurred in an individual who lived alone and was found unresponsive in his apartment. All cases occurred between May and August. Seven patients were male, and the median age was 31 years (range 22-45 years). All patients were previously healthy without medical co-morbidities. The median temperature at presentation was 40.7°C (IQR 40.6-42.2°C). Two patients entered the ALFSG registry without documented temperatures >40°C, but were later classified as heat stroke by the site investigator after other ALF causes were ruled out. All patients tested negative on a urine drug toxicology screen. Grade 3 or 4 hepatic encephalopathy was present in 80% of patients with ALF. Five patients initially presented to an outside emergency department (ED) and were transferred to an ALFSG study site for higher level of care (median time to transfer 2.5 days [range 1-8 days]).

3.2 | Laboratory values on admission

Three patients had normal liver enzymes at ED presentation prior to study enrolment. Liver injury was very severe in all cases, with a mixed hepatocellular and cholestatic pattern. Seven of eight patients developed acute kidney injury, and all eight had lactic acidosis and rhabdomyolysis. When compared with ALI or ALF patients from APAP or ischaemia, patients with heat stroke were younger, mostly male, and had similar blood pressure on admission but had more severe liver

injury, thrombocytopaenia and elevated serum creatinine, lactate and creatine kinase (Table 1). Ammonia levels were recorded in six patients on admission (median 50.5 μmol/L [IQR 29-70.5 μmol/L) with the maximum value being 130 μmol/L in a patient with spontaneous survival.

3.3 | Management

Six patients underwent documented cooling protocols. All patients were admitted to the intensive care unit (ICU) at the study site. Each patient achieved normothermia, defined as temperature <38°C, within 24 hours of study enrolment. The majority of patients had stable haemodynamics throughout admission, but two patients required vasopressors. Three patients required mechanical ventilation, three received N-acetyl cysteine (NAC), three underwent renal replacement therapy (RRT), one had an intracranial pressure monitor (ICP) placed and none received mannitol.

3.4 | Outcomes

Five patients recovered with supportive care alone, although one had been initially listed for LT. One patient underwent combined kidney/liver transplantation because of persistent anuric renal injury requiring 3 weeks of RRT and was alive at 1 year of follow-up. Two patients died—both within 48 hours of admission from multi-organ system failure. In the first case, the patient was attempting to lose weight by taking dietary supplements, diuretics and running on a treadmill wearing a sweat suit wrapped in plastic. His initial temperature was 42.2°C and was cooled but had a rapidly deteriorating clinical course requiring mechanical ventilation, vasopressors and RRT. The second patient found unconscious in his apartment with a temperature of 42.2°C. He underwent cooling but required vasopressors, mechanical ventilation, RRT and ICP monitor placement for persistently impaired mental status, which showed normal measurements. He was not deemed a candidate for LT. Histopathology of the CHS case at

TABLE 1 Comparison of patients presenting with acute liver injury or failure (ALI/ALF) secondary to heat stroke, APAP, or ischaemia. Baseline values are compared with laboratory values on admission and peak values during study enrolment

	Heat Stroke (n=8)		APAP (n=1289)		ischaemia (n=152)	
ALI/ALF Aetiology	**N**	**Median (IQR)**	**N**	**Median (IQR)**	**N**	**Median (IQR)**
Baseline characteristics						
Age (year)	8	31.0 (25.5-35.5)	1289	36.0 (27.0-46.0)	152	53.0 (39.0-60.0)
Sex (%)	8	Male (87.5)	1289	Male (25.8)	152	Male (44.1)
Race (%)	8	White (100.0)	1289	White (85.0)	152	White (77.6)
Maximum Temp (°C)	8	40.7 (40.6-42.2)	1262	37.1 (36.7-37.6)	148	36.9 (36.5-37.4)
MAP	8	90.8 (85.0-93.3)	1282	87.7 (76.3-98.7)	152	86.8 (73.0-99.0)
Laboratory Values on Admission						
Platelet (10^3/μL)	8	45.5 (35.5-67.5)	1270	129.0 (88.0-185.0)	151	88.0 (55.0-129.0)
INR	8	3.5 (2.9-4.3)	1258	2.8 (2.0-4.3)	150	2.4 (1.9-3.2)
AST (IU/L)	8	5179.0 (1784.5-9897.5)	1279	3963.0 (1599.0-7821.0)	152	2570.5 (1061.5-5850.0)
ALT (IU/L)	8	6092.0 (3882.5-8811.5)	1278	3993.0 (2087.0-6537.0)	151	2178.0 (1288.0-4260.0)
ALP (U/L)	8	109.5 (82.0-137.0)	1258	115.0 (88.0-154.0)	148	36.9 (36.5-37.4)
Total Bilirubin (mg/dL)	8	8.8 (5.8-10.7)	1274	4.1 (2.4-6.1)	151	3.8 (2.2-6.6)
sCr (mg/dL)	8	2.4 (1.4-6.0)	1284	1.5 (0.8-3.0)	152	2.4 (1.4-3.7)
CK (U/L)	8	3662.0 (2501.0-41250.0)	385	365.0 (149.0-1425.0)	83	578.0 (141.0-2506.0)
Lactate (mg/dL)	8	6.7 (5.6-12.4)	757	3.8 (2.2-8.2)	104	3.7 (2.4-7.1)
Peak Values During Admission						
INR	8	4.2 (3.0-4.6)	1276	3.0 (2.1-4.7)	151	2.5 (1.9-3.6)
AST (IU/L)	8	5179.0 (1784.0-9897.5)	1287	4500.0 (1900.0-8500.0)	152	2764.0 (1083.5-6016.0)
ALT (IU/L)	8	6092.0 (4259.0-8811.5)	1285	4400.0 (2426.0-6970.0)	152	2257.5 (1326.5-4316.5)
ALP (U/L)	8	123.0 (99.0-198.5)	1264	126.0 (94.0-168.0)	148	141.5 (102.0-227.5)
Total Bilirubin (mg/dL)	8	12.9 (11.0-25.9)	1284	6.2 (3.4-10.7)	152	5.6 (2.8-12.2)
sCr (mg/dL)	8	4.3 (1.4-6.4)	1287	1.9 (0.9-4.4)	152	2.7 (1.6-4.9)
CK (U/L)	8	12346.0 (2626.0-48770.0)	420	373.0 (150.5-1431.5)	93	607.0 (129.0-2753.0)
Lactate (mg/dL)	8	8.8 (6.7-13.1)	842	3.9 (2.2-8.6)	112	3.8 (2.5-7.8)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; CK, creatine kinase; INR, international normalized ratio; MAP, mean arterial pressure; sCR, serum creatinine.

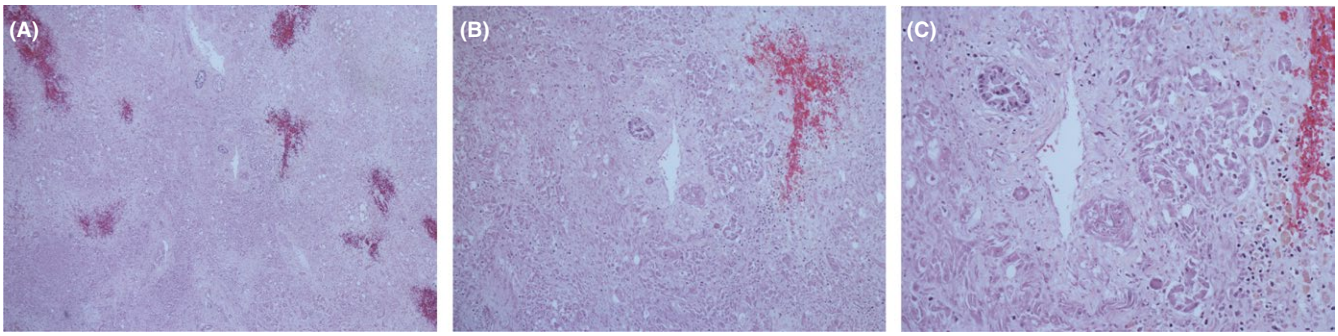

FIGURE 1 Autopsy histopathology of the liver in a patient who died from heat stroke and acute liver failure: (A) massive hepatocyte necrosis throughout nearly the entire lobule, ×40; (B, C) Showing viable bile duct in portal tract, rare viable hepatocytes in periportal zone, haemorrhagic necrosis in centrilobular zone, picture B at ×100, C at ×200. Autopsy was performed within 6 hours of death

autopsy demonstrated massive hepatocellular necrosis, with centrilobular haemorrhage (Figure 1).

Overall, the median length of stay in the series was 5 days (IQR 2.75-38.25 days). No long-term sequelae were observed in survivors at 1 year of follow-up and all laboratory abnormalities returned to normal.

4 | DISCUSSION

Our series demonstrates that heat stroke is a rare cause of ALF. All but one of our cases occurred in young, previously healthy males enduring excessive exertion during summer months. Most cases occurred outdoors after long distance running, with distances ranging from 5 to 20 km. While TFS was the most frequent outcome, ALF from heat stroke can be fatal, and both deaths were attributed to multi-organ system failure. Factors that portend a poor prognostic outcome included temperature >42°C, rapid multi-organ failure requiring artificial organ support, and circulatory collapse requiring vasopressors.

In our series, management of heat stroke and ALF focused on supportive care with one case undergoing successful liver transplantation. Initial treatment should concentrate on cooling protocols, with the goal of achieving normothermia within 6 hours. While specific cooling protocols were not documented in these cases, as patients were enrolled in the ALFSG registry after ED resuscitation, previous studies on EHS patients indicate the best method for cooling involves immediate cold water immersion at very cold temperatures (1-14°C) or ice water.[15] Hepatocellular injury may be delayed by up to 24 hours, as several patients in our series had normal chemistries on presentation. In patients who develop worsening coagulopathy or encephalopathy, transfer to centres with expertise in organ transplantation should be considered.

It is important for the clinician to maintain a high index of suspicion for ALI or ALF in a patient with heat stroke as the diagnosis of ALF and heat stroke overlap with respect to altered mental status. For instance, a patient's persistent encephalopathy after heat stroke may be the first clinical sign of acute liver failure.

All patients with heat stroke and ALI/ALF should be admitted to an ICU for close monitoring, as supportive care of ALF patients in the ICU has improved TFS and overall survival over the past decade.[16]

The mechanisms that lead to multi-organ failure in heat stroke remain unclear, but studies suggest the systemic inflammatory response (SIRS) plays a critical role in cellular injury after heat exposure by activating pathways leading to cellular necrosis and apoptosis.[17] Heat stroke has been shown to induce liver injury in rats via the interlukin-1B pathway.[18] The tissues most sensitive to changes in temperature are brain and liver, but heat also damages kidney, myocardium, muscle and the gastrointestinal tract. Ischaemic hepatitis may also develop related to vascular collapse from dehydration and shunting of blood from the splanchnic circulation to the skin in order to dissipate heat.[2] Thrombocytopaenia, as seen in all our patients, is associated with SIRS activation and poor prognosis in ALF patients.[19]

Future therapies designed to target the inflammasome, such as high-volume plasma exchange (HVP), could be promising in patients with heat stroke and ALF. HVP was successful in a single individual who develop CHS and ALF after prolonged sauna exposure[20] and improved TFS in an open-label randomized trial of 182 ALF patients.[21]

5 | CONCLUSIONS

Heat stroke is a rare, but severe and potentially fatal cause of ALF—frequently because of over-exertion by young males in early summer months. Prompt recognition and measures to prevent such occurrences should be stressed to medical providers and public health officials.

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CONFLICTS OF INTEREST

The authors disclose no conflicts.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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