CASE REPORT

Liver transplantation for non-exertional heat stroke-related acute liver failure

Sandra Coenen,¹ Khe Tran,² Jubi de Haan,³ Rob de Man¹

¹Department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

²Transplant Surgery Erasmus MC, Rotterdam, Zuid-Holland, The Netherlands

³Adult Intensive Care Erasmus MC, Rotterdam, Zuid-Holland, The Netherlands

Correspondence to
Sandra Coenen,
s.coenen@erasmusmc.nl

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SUMMARY

Heat stroke is a life-threatening condition characterised by hyperthermia leading to multiple organ dysfunction. Acute liver failure is a rare and potentially fatal consequence of heat stroke. Management of heat stroke is mainly supportive but liver transplantation can be considered as the treatment of acute liver failure in heat stroke. However, literature on liver transplantation as a treatment for acute liver failure in heat stroke is scarce. Until now, no cases of liver transplantation for acute liver failure in non-exertional heat stroke have been reported. Here, we present the first case report of a successful liver transplantation in a patient with acute liver failure caused by non-exertional heat stroke after a sauna visit.

BACKGROUND

Heat stroke is a potentially fatal disorder characterised by a rise in body temperature above 40°C that is associated with a systemic inflammatory response leading to multiple organ dysfunction in which central nervous system dysfunction predominates.¹ Traditionally, heat stroke is classified into two groups according to aetiology. Classical or non-exertional heat stroke is caused by exposure to a high environmental temperature. Exertional heat stroke results from strenuous exercise, both in combination with the inability of the patient to maintain thermoregulation, for example, due to excess clothing, dehydration or drug use. The pathophysiology of heat stroke is not fully understood. The current model proposes that it results from thermoregulatory failure followed by an exaggerated acute phase and altered heat shock response.^{2,3} The consecutive interplay between the cytotoxic effect of the heat and the inflammatory and coagulation responses results in multiple organ failure.^{1,4,5}

Acute liver failure (ALF) is a rare and life-threatening condition triggered by sudden hepatic injury giving rise to hepatic necrosis and subsequent multiple organ failure. In order to dissipate the heat, cutaneous vasodilatation occurs and splanchnic vasoconstriction occurs resulting in a redistribution of blood flow to the skin. This may lead to splanchnic hypoperfusion and (hepatic) ischaemia.¹ Diffuse intravascular coagulation may further contribute to hepatic failure.

ALF has been observed in up to 5% of patients with exertional heat stroke.^{6,7} Liver transplantation is considered life-saving in critically ill patients with acute liver failure. However, literature on liver transplantation as a treatment for ALF in exertional

heat stroke is scarce.⁸ Until now, no cases of liver transplantation for ALF in non-exertional heat stroke have been reported. This is the first case report describing a successful liver transplantation in a patient with ALF caused by non-exertional heat stroke after a sauna visit.

CASE PRESENTATION; INCLUDING INVESTIGATIONS, TREATMENT OUTCOME AND FOLLOW-UP

A previously healthy 69-year-old Caucasian male was admitted to the emergency department of a referral hospital after he was found unconscious in a dry air hot sauna cabin of approximately 90°C. The time he stayed in the sauna before he was found is unknown but was estimated at 90 min. On arrival at the emergency room, he was unconscious with a score of 5 on the Glasgow Coma Scale and had a rectal temperature of 40.3°C. His blood pressure was 80/40 mm Hg with a pulse of 150 beats per minute. He presented with second-degree burns and pressure sores on his nose, knees and toes. Immediate management included resuscitation with intravenous saline, acetaminophen (2 doses of 1000 mg on the first day of admission) and external cooling with ice packs. He was sedated, intubated for mechanical ventilation and admitted to the intensive care unit where his condition initially stabilised. His body temperature normalised to 37.7°C within 1 hour. Daily laboratory results are shown in [table 1](#). The haemoglobin, leucocytes, triglycerides and C reactive protein were normal. The thrombocytes were $50 \times 10^9/L$ on admission.

On the third day his condition deteriorated. He required vasopressors to maintain adequate blood pressure and his consciousness deteriorated to a Glasgow Coma Scale of 3. Laboratory studies showed evidence of liver failure and diffuse intravascular coagulation ([table 1](#)). The patient was subsequently referred to the intensive care unit of our hospital for specialised treatment and evaluation for liver transplantation. Because of evidence of mild rhabdomyolysis (maximum level of creatine kinase of 3429 U/L) with acute kidney injury ([table 1](#)), aggressive fluid hydration was continued and continuous renal replacement therapy was started. Acetylcysteine and broad-spectrum antibiotics were started together with a selective gut decontamination regimen.

The patient's medical history was negative for alcohol and drug abuse or (alternative) medication use. There was no serological evidence for acute

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Table 1 Laboratory results on days of admission

	Reference values	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Creatinine (μmol/L)	<115	168	132	183	309	319	234	250	296
Bilirubin total (μmol/L)	<17	29	47	50	66	102	148	40	23
ASAT (U/L)	<35	74	4335	12 688	12 669	4739	1480	1371	485
ALAT (U/L)	<45	45	3966	10 100	10 857	6941	4716	2643	1665
INR	1.0	2.1	4.3	>10	>10	5.7	3.4	1.6	1.3
D dimer (mg/L)	<0.5	–	>35	79.8	–	–	–	–	–
Fibrinogen (g/L)	1.5–3.6	0.5	0.4	0.2	0.2	0.3	0.6	2.3	2.9
Creatine kinase (U/L)	<171	2507	3429	2898	2626	1371	–	–	–

Day 3 of admission is the day of listing for liver transplantation, day 6 is the day of transplantation.

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; INR, international normalised ratio.

or chronic hepatitis A, B, C and E. HIV, acute cytomegalovirus, herpes simplex virus and Epstein-Barr virus infection were excluded. Autoimmune serology (antinuclear antibody (ANA), antimitochondrial antibody (AMA), antismooth muscle antibody (SMA), antisoluble liver antigen antibody (anti-SLA), antiliver kidney microsomal (anti-LKM) type 1 antibody, IgM and IgG), α 1 antitrypsin, ceruloplasmin and serum copper were all within the normal range. Drug screening performed on the second day of admission showed an acetaminophen level of 16.8 mg/L (16 hours after administration; level is within the normal range), probably due to the acetaminophen given on admission because of hyperthermia. There was no history of acetaminophen use before admission. No sedative medication was prescribed in the months before admission.

An ECG and echocardiogram showed no signs of cardiac ischaemia. Brain CT excluded intracranial haemorrhage and other structural abnormalities. Abdominal ultrasound and CT imaging showed no signs of liver or abdominal vascular pathology or other abdominal abnormalities.

On the day the patient was referred to our hospital (day 3), he met the King's College criteria⁹ for liver transplantation in ALF and was listed for high urgency liver transplantation. On day 6 after initial presentation, the patient underwent an uncomplicated liver transplantation of a deceased brain-dead donor.

The explanted liver weighed 1564 g. The capsule was flattened and on macroscopic sections the liver showed a yellow-tan to light-brown, focally mottled, aspect with obvious extinction

of the parenchyma. The periphery of the specimen showed some areas with still viable liver tissue (figure 1).

Microscopic examination showed widespread hepatocellular loss with confluent necrosis, collapse and condensation of the underlying reticulin framework, accompanied by outgrowth of periportal bile ductular structures. Inflammation was not prominent. Sinusoids were variably congested and sometimes there was extravasation of red blood cells. There was no fibrosis and not obvious steatosis. No regenerative nodules were found (figure 2).

Immunosuppressive medication was started according to local protocol with prednisolone and mycophenolate mofetil directly after transplantation, basiliximab on postoperative day (POD) 0 and 4 and tacrolimus from POD 5 onwards.

After transplantation, the liver function gradually improved and normalised within 4 days (table 1). Initially, the patient showed an agitated delirium after lowering the sedatives. As his mental status improved on day 1, sedatives could be stopped and the patient was extubated on POD 2. There were no signs of any neurological sequelae. Continuous renal replacement therapy was discontinued on POD 4 and renal function normalised on POD 13. On POD 6, the patient was transferred to the ward. No infectious complications occurred.

The patient was discharged on POD 20 and is currently still free of complications at 10 months after liver transplantation.

Figure 1 Macroscopy of the liver explant cut section of explanted liver. There is some vital liver tissue at the periphery (arrows). Centrally, the specimen shows extinction of the parenchyma (lined area).

Figure 2 Microscopy of the liver explant. Microscopic image of necrotic lobular parenchyma (lined areas) and extended ductular reaction (arrows). Note the absence of hepatocytes (H&E x200).

DISCUSSION

We describe a case of a previously healthy man who developed a non-exertional heat stroke followed by ALF after a sauna visit. On day 6 after initial presentation, the patient underwent an uncomplicated liver transplantation. To the best of our knowledge, this is the first case report describing successful liver transplantation in a patient with ALF caused by non-exertional heat stroke after a sauna visit.

Heat stroke is characterised by a rise of body temperature above 40°C that is associated with a systemic inflammatory response leading to a syndrome of multiple organ failure in which central nervous system dysfunction predominates.¹ Classical or non-exertional heat stroke is caused by prolonged exposure to a high environmental temperature like a sauna or a hot spring visit. Exertional heat stroke results from strenuous exercise. Heat stroke is associated with high rates of morbidity and mortality (in hospital mortality of 58%).^{10 11} Residual brain damage is present in 20% of the surviving patients and is associated with high mortality.¹¹

Increased liver enzymes and liver dysfunction are commonly observed in heat stroke,¹² whereas ALF is rare and has only been documented in up to 5% of patients with exertional heat stroke.^{6 7} Elevation of serum transaminases is the most common liver test abnormality in heat stroke with a peak between days 3 and 5.¹² It should be mentioned that rhabdomyolysis, which is also frequently seen in heat stroke, can also give rise to elevation of serum transaminases. In this case, the discrepancy between the rise in liver transaminases and the rise in creatine kinase suggests that the rhabdomyolysis plays a minor role in the elevation of the serum transaminases. To support this, liver transaminases continued to rise as creatine kinase activity already was decreasing. Furthermore, viral hepatitis, drug-induced liver failure, alcohol, Budd-Chiari syndrome, Wilson's disease, α 1 antitrypsin deficiency and autoimmune hepatitis (AIH) were also considered in the differential diagnosis of ALF in this case. Virology, laboratory testing and abdominal imaging showed no evidence of acute or chronic viral hepatitis, Wilson's disease, α 1 antitrypsin deficiency or Budd-Chiari syndrome. As mentioned, the patient's medical history was negative for alcohol or drug abuse or (alternative) medication use. However, drug screening performed on the second day of admission was positive for acetaminophen. Since the level was within the normal range and the patient's medical history was negative for chronic

acetaminophen use, this was probably due to the acetaminophen given on admission. Therefore, in this case acetaminophen intoxication as the cause of ALF was considered unlikely. Normal autoimmune serology (including ANA, AMA, SMA, anti-SLA, anti-LKM type 1, IgM and IgG levels) makes AIH as a cause for ALF in this case less likely. However, it should be kept in mind that in patients with an acute presentation of AIH, IgG levels, ANA and/or SMA may be negative.¹³ In addition, in ALF the clinical relevance of non-organ-specific autoantibodies like ANA, SMA and anti-LKM and disease-specific autoantibodies like anti-SLA remains uncertain. It was shown that in patients with ALF caused by non-acetaminophen-induced drug reactions and hepatotropic viral infections, non-organ-specific autoantibodies were prevalent in 25% and anti-SLA in 30% of the cases.¹⁴ This suggests that the presence organ and non-organ-specific antibodies may reflect active and severe liver injury in the presence of immunological activation. Differentiating ALF caused by AIH from other aetiologies is also complicated by the fact that classical histological features of AIH (portal tract necro-inflammatory process with interface hepatitis and often with lobular involvement) may not be present in ALF due to AIH.¹⁵ Furthermore, liver histology in ALF due to AIH is sometimes indistinguishable from other causes of ALF.¹³ In this case, AIH as a cause for the ALF was considered unlikely but cannot be excluded based on the absence of autoantibodies, normal IgG levels and absence of typical features of AIH on liver histology.

In ALF, liver transplantation is the only possible treatment. However, the prognosis of patients with ALF after heat stroke is unpredictable and there is limited experience with liver transplantation in ALF caused by heat stroke. Therefore, based on the data in literature the indication and relative contraindications for liver transplantation in this setting are unclear.

ALF following non-exertional heat stroke is rare. Dematte *et al* described 58 patients with non-exertional heat stroke during the Chicago heat wave of 1995, but none of them developed ALF.¹⁶ To our knowledge, eight adult cases of ALF after non-exertional heat stroke have been described in English literature. These cases are summarised in table 2.^{7 17–23}

Half of the cases were fatal. Four patients survived with conservative treatment. One of these patients was successfully treated with high volume plasma exchange.²² None of the patients underwent liver transplantation. Three of these patients however, did meet the King's College criteria for liver

Table 2 Published cases of patients with non-exertional heat stroke and acute liver failure

	Age years/ sex	Cause	Temperature (°C)	Peak bilirubin (μ mol/L)	INR	King's College criteria	LT	Survival	Remarks
Weigand <i>et al.</i> (⁷)	46/ ♂	Sun	42	32; day 1	1.9; day 1	No	No	Yes	
Siegler (¹⁷)	UK/ ♀	Sauna	UK	UK	UK	UK	No	No	Underlying Hashimoto's thyroiditis
Kim <i>et al.</i> (¹⁸)	68/ ♂	Bath	41	906; day 25	7.6	Yes	No	No	Died on day 25 of septic shock
Deutsch <i>et al.</i> (¹⁹)	30/ ♂	Shipment	42	90; day 7	2.8; day 7	No	No	Yes	
Akieda <i>et al.</i> (²⁰)	73/ ♂	Bath	39.7	564; day 13	4.8; day 2	No	No	Yes	
Lee <i>et al.</i> (²¹)	57/ ♂	Hot spring	41	521; day 7	1.8 day 7	Yes	No	No	Received MARS Died on day 65 of septic shock
Eraslan <i>et al.</i> (²²)	63/ ♂	Sauna	40	133; day 6	9.5; day 6	Yes	Listed	No	Died while listed on day 6
Chen <i>et al.</i> (²³)	73/ ♂	Sauna	41.7	191; day 6	UK	UK	No	Yes	Received high volume plasma exchange
Current report	69/ ♂	Sauna	40.3			Yes	Yes	Yes	

INR, international normalised ratio; LT, liver transplantation; MARS, Molecular Adsorbent Recirculation System; UK, unknown.

transplantation in ALF. For the patient reported by Kim *et al*, it has not been described why liver transplantation was not considered.¹⁸ The patient described by Lee *et al* met the King's College criteria but was treated with Molecular Adsorbent Recirculation System.²¹ The patient died of septic shock after 65 days. One patient meeting the criteria was listed for transplantation but died on day 6 while on the waiting list.²² Our patient met the King's College criteria for liver transplantation in ALF and is the first documented case to undergo liver transplantation for non-exertional heat stroke. He is still alive without any remarkable comorbidity 10 months after transplantation.

The extent and progression of liver damage vary in the reported cases. The decision to list for liver transplantation in heat stroke is complicated by the fact that several prognostic factors used to assess the severity of liver failure such as level of consciousness and coagulation status can be confounded by the symptoms of the heat stroke and may not reflect the degree of liver injury. The disturbances of coagulation tests as a decrease in liver synthesis might be overestimated because of concomitant diffuse intravascular coagulation and impaired consciousness does not necessarily indicate liver-related encephalopathy. Therefore, it would be useful to develop a prognostic scoring system to appropriately stratify the severity of organ failure in heat stroke and predict the mortality. This would help to identify the patients benefiting from liver transplantation and improve outcomes. However, development of such a scoring system would be difficult since heat stroke-associated liver failure is rare.

Learning points

- ▶ Exertional as well as non-exertional heat stroke may be complicated by acute liver failure and is associated with a high mortality rate.
- ▶ Although full recovery with conservative management has been described, liver transplantation should be considered for those with acute liver failure.
- ▶ Further clinical experience is needed to weigh the risk and benefit of liver transplantation or conservative management to treat acute liver failure in heat stroke.

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