Lessons from practice

Management challenges and prognostic uncertainties in heat-induced acute liver failure

Clinical record

A 26-year-old man with central obesity (body mass index, 32.7 kg/m^2) and a history of drinking up to 22 standard drinks over weekends, collapsed 5 minutes following a 5 km run in hot and humid conditions in Brisbane, Australia. He was not on any regular medications or supplements and had been running 3 km, four times weekly, for the previous four months. He presented to a tertiary hospital with a Glasgow Coma Score of 10, hyperthermia (40.6°C), acute kidney injury and rhabdomyolysis. After resuscitation, cooling and intubation, he was transferred to the Intensive Care Unit (ICU) and treated with noradrenaline to maintain mean arterial pressure over 65 mmHg and broad-spectrum antibiotics. The patient was extubated on Day 2 with a stable Glasgow Coma Score of 14. From Day 3, his creatinine level rose to 482 µmol/L (reference interval [RI], 60–110 µmol/L), requiring renal replacement therapy and his liver function markedly worsened (see Box 1 and Box 2). Common causes of acute hepatitis (viral, autoimmune, drug-induced) were excluded with laboratory testing and further history.

On Day 4, he developed disseminated intravascular coagulation marked by an international normalised ratio exceeding 10 (RI, 0.9–1.2), clottable fibrinogen below 0.04 g/L (RI, 2.0–4.5 g/L), D-dimer level over 128 mg/L (RI, 0.02–0.48 mg/L) and platelet

1 Laboratory findings and timeline

	Bilirubin (µmol/L)	ALP (U/L)	GGT (U/L)	ALT (U/L)	AST (U/L)	LDH (U/L)	Platelets (x10^9/L)	INR	Fibrinogen (g/L)	Creatinine (µmol/L)	CK (U/L)	Lactate (mmol/L)
Reference interval	< 20	30–110	< 55	< 45	< 35	120–250	140–400	0.9–1.2	2.0–4.5	60–110	46–171	0.5–2.2
Day												
1	4	132	68	77	82	421		0.9	3.0	168	426	12.4
2	4	133	67	78	216	656				215	1450	1.8
3	26	172	124	2860	4450	550	48	3.8	1.8	482	12 900	3.3
4 (am)	90	207	150	7550	12 800	11 015	43	3.7	1.0	523	2750	6.1
4 (pm)	132	185	134	9200	11 900	11 914	19	> 10	< 0.4	470	5110	8.2
5	136	169	117	6170	7800	8174	53	2.4	1.3	373	74 100	5.4
6	118	146	98	4520	2810	2641	31	2.8	0.8	372	45 200	1.8
8	109	137	82	2080	883	891	47	1.6	1.1	353	12 900	1.5
9	110	143	93	1500	620	708	116	1.1	2.5	674		1.6
10	104	136	155	739	233	492	165	1.1	3.7	858		
11	106	143	195	541	198	509	205	1.1	4.0	1110		
12	96	140	214	443	184	456	208			830		
15	84	160	345	361	266	589	353	1.0	4.8	1150	2710	
16	62	230	690	354	285	640	381			1000		
17	61	262	813	348	292	676	347	0.9	5.7	736	2320	
18	54	272	807	333	262	673	335			399	1940	
19	49	277	810	310	263	666	397			529	2610	
21	34	216	609	242	321	625	400			287	3820	
23	33	234	625	260	366	671	440	0.9	5.6	240	3760	
25	31	185	504	248	412	663	399	1	5.4	189	4610	
26	23	142	363	201	287	607	354	1	5.3	144	2330	
31	25	152	389	207	279	623	378	1	5.3	128	2320	
57	8	110	165	112	50	230	314	0.9		75		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = γ-glutamyltransferase; INR = international normalised ratio; LDH = lactate dehydrogenase. ◆

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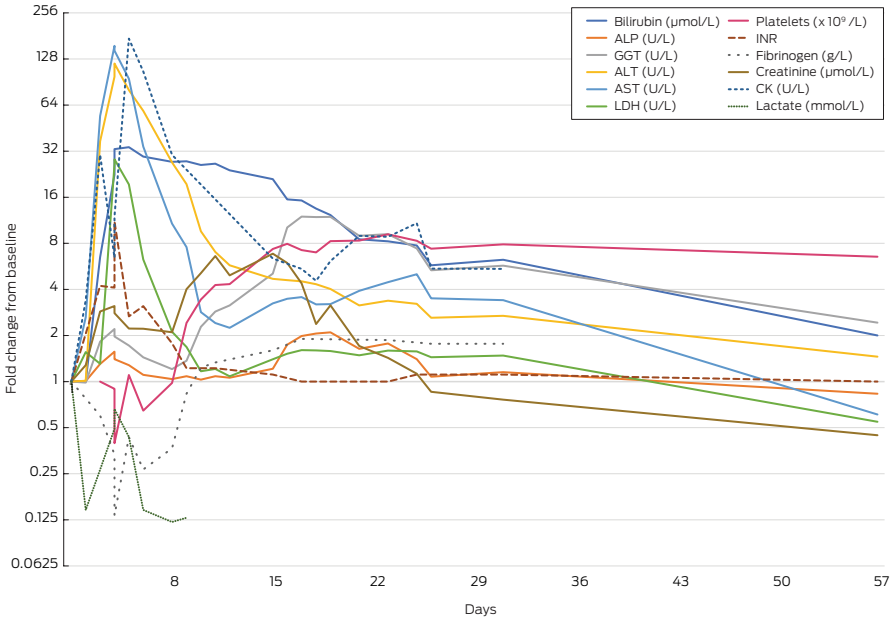
2 Fold change of laboratory values from initial value over time



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = γ-glutamyltransferase; INR = international normalised ratio; LDH = lactate dehydrogenase. ◆

count of 19×10^9/L (RI, 140–400 × 10^9/L). His lactate dehydrogenase level peaked on Day 4 at 11 914 U/L (RI, 120–250 U/L). He had evidence of asterixis with a venous ammonia level of 110 μmol/L (RI, < 50 μmol/L) and altered cognition consistent with acute liver failure (ALF). Treatment included N-acetyl cysteine infusion, rifaximin and lactulose. His coagulation profile was supported with cryoprecipitate, fresh frozen plasma and three-factor (II, IX and X) prothrombin complex concentrate (Prothrombinex-VF, CSL Behring). His creatinine kinase concentration peaked on Day 5 at 74 100 U/L (RI, 46–171 U/L). He was transferred to the ICU at the local liver transplant centre on Day 5.

With supportive care, he avoided transplantation and his liver function steadily improved (encephalopathy resolved on Day 6, international normalised ratio stabilised on Day 9). He was discharged from the ICU on Day 8 but his cholestatic enzymes began to rise reaching a peak alkaline phosphatase concentration of 277 U/L (RI, < 110 U/L) and γ-glutamyltransferase concentration of 810 U/L (RI, < 55 U/L) on Day 19. A magnetic resonance cholangiopancreatogram showed a diffuse reduction in intrahepatic bile duct calibre. Cholestasis improved with ursodeoxycholic acid and his bilirubin level normalised by Day 57. Dialysis had ceased on Day 20. At the four-month follow-up, he remained fatigued but otherwise well. His metabolic screen was negative.

Discussion

In Australia from 2006 to 2019, extreme heat caused 252 deaths, with an additional 170 deaths contributed to by extreme heat.[1] Heatstroke is a life-threatening condition associated with an uncontrolled rise in core body temperature above 40°C. This occurs due to the failure of the body's compensatory mechanisms required to maintain thermal homeostasis. Classic heatstroke results from passive exposure to high temperatures and humidity, often during heatwaves and primarily affects the older population. Exertional heatstroke (EHS) tends to affect younger, healthier individuals during vigorous exercise. The prevalence of EHS is unknown and often underestimated.[2]

The pathophysiology of heatstroke is complex, resulting most commonly in brain dysfunction; however, in severe cases, patients may develop disseminated intravascular coagulation, circulatory shock, pulmonary oedema and acute kidney injury.[3] Muscle breakdown in rhabdomyolysis causes elevated concentrations of transaminases, potentially obscuring the early signs of underlying liver injury. ALF is a rare but life-threatening complication of EHS, resulting from severe hyperthermia-induced direct liver injury, ischaemia, systemic inflammatory response, coagulopathy and multiorgan dysfunction. Management of EHS involves rapid implementation of cooling protocols and supportive care, including stabilising vital signs, maintaining adequate hydration and providing respiratory and circulatory support. The management of EHS complications involves organ support similar to that used in trauma or sepsis with liver transplantation used in cases of fulminant liver failure.[4]

The literature on EHS-induced ALF and its treatment is primarily based on heterogenous case reports, making it challenging to predict which patients will not survive with supportive management alone. Although liver transplantation is a preferred treatment option in selected cases, some patients who meet the transplant criteria, such as the patient discussed herein, also recover spontaneously.[5,6] The use of King's College criteria to identify severe cases with poor prognosis without liver transplantation is limited due to unique pathophysiology of EHS-induced ALF.

Liver transplantation alone does not address other organ failures, emphasising the importance of ongoing ICU care and raising considerations about the timing of transplantation decisions.[7] With climate change potentially leading to a rise in such incidents,[8] it is imperative to address heatstroke-induced liver failure from both medical and public health perspectives.

From a medical standpoint, the focus should be in improving the understanding of this condition, prompt recognition of cases, prioritisation of comprehensive patient care in ICU and development of enhanced risk stratification tools to ensure favourable patient outcomes.

Lessons from practice

- Heatstroke is a life-threatening condition that occurs when the body temperature rises above 40°C due to failed thermal regulation.
- Heatstroke can lead to extreme and life-threatening complications, such as acute liver failure, which requires comprehensive management, including liver transplant in severe cases.
- The King's College criteria for severe cases may not apply to heatstroke-induced acute liver failure due to multiorgan involvement, highlighting the need for better risk stratification.
- Climate change may increase the incidence of these cases, necessitating a better understanding of the condition, prompt management and improved public health strategies.

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