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BRIEF REPORT

Therapeutic plasma exchange in the treatment of exertional heat stroke and multiorgan failure

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Abstract
Background Exertional heat stroke (EHS) results in a constellation of systemic inflammatory responses resulting in multiorgan failure and an extremely high mortality.
Case Diagnosis and Treatments We present the case of an 11-year-old obese male who suffered EHS with rhabdomyolysis and concurrent renal, pulmonary, and hepatic failure. Conventional therapies including continuous veno-venous hemodiafiltration (CVVHDF) were ineffective in preventing ongoing deterioration in clinical status. Liver biopsy was reported as "extensive hepatocyte ballooning" and liver-kidney transplantation was tentatively planned.
Conclusions The addition of therapeutic plasma exchange using the Prismaflex® system (Gambro, Lakewood, CO, USA) resulted in a reversal of the inflammatory process and recovery from multiorgan failure. Liver biopsy was not a reliable indicator of irreversible hepatic injury.

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Keywords Therapeutic plasma exchange · Heat stroke · Continuous renal replacement therapy

Introduction

Exertional heat stroke (EHS) is the most extreme entity in the spectrum of heat-related illnesses [1]. It has traditionally been defined as a core body temperature above 40–40.6 °C (104 to 105 °F) accompanied by a systemic inflammatory response leading to multiorgan dysfunction with predominant encephalopathy [2]. The standard treatment for EHS includes aggressive cooling and supportive measures such as alkalinization of urine to prevent rhabdomyolysis induced renal injury, hemodialysis, mechanical ventilation, correction of coagulopathy, and seizure control [3]. Despite these efforts, EHS mortality is high and is usually associated with multiorgan failure, especially coagulopathy and hepatic injury [4–6]. In this report, we describe a case of EHS in an obese 11-year-old male treated with concomitant continuous veno-venous hemodiafiltration (CVVHDF) and therapeutic plasma exchange (TPE).

Case report

An 11-year-old African American male who was visiting southern Florida for the summer went for a jog in the late afternoon but developed muscle cramps after 1.5 miles. When he arrived home, he felt short of breath and weak. He soon collapsed and emergency medical services were called. When they arrived, he was conscious but confused with poor respiratory effort. His core temperature was 107 °F, and he was hypotensive. He was intubated and aggressively cooled with

fluid resuscitation. His initial serum studies demonstrated a metabolic acidosis, lactic acidemia, elevated transaminases, thrombocytopenia, and elevated creatine phosphokinase (CPK). He was subsequently transferred to the tertiary care hospital, and continued to be hyperthermic with significantly low blood pressure requiring pharmacologic vasopressor support, colloid and crystalloid administration. Repeat laboratory parameters demonstrated thrombocytopenia, rising transaminases, hyperammonemia, and disseminated intravascular coagulopathy. Elevated CPK, to as high as 4,745 U, indicated rhabdomyolysis. Renal failure rapidly ensued with oliguria despite diuretic therapy.

As the patient became progressively fluid overloaded with evidence of pulmonary edema, pleural effusion, and worsening pulmonary compliance, we initiated continuous veno-venous hemodiafiltration (CVVHDF) on hospital day 2 using the Prismaflex® continuous renal replacement therapy (CRRT) system with the M60 filter.

With CVVHDF initiation, the patient's fluid status improved but he remained critically ill with depressed mental status. His liver function continued to deteriorate, with refractory coagulopathy, thrombocytopenia, and a low A disintegrin and metalloprotease with thrombospondin motifs-13 (ADAMTS-13) level at 46 % after having received multiple infusions of fresh-frozen plasma (FFP). Therapeutic plasma exchange (TPE) was added on hospital day 3. The same Prismaflex® system was used with the TPE-2000 filter with 1.25 to 1.5 volume exchange using FFP. On day 5, with little improvement in laboratory parameters, there was concern for encephalopathy. The patient was weaned off all sedatives but remained obtunded and unresponsive to pain maneuvers. An electroencephalogram showed diffuse cerebral dysfunction and a computed tomography scan of the brain without contrast did not reveal any anatomic abnormality. He developed persistent hyperbilirubinemia and worsening hyperammonemia, despite enteral lactulose and neomycin. A liver biopsy was obtained via a trans-jugular approach. This showed both intracellular and canalicular cholestasis with 100 % ballooning of hepatocytes and acute periportal inflammation. Subsequently, the patient was listed for a combined liver-kidney transplant with re-evaluation on a day-to-day basis.

Nevertheless, TPE was continued daily while awaiting transplantation. With the eighth session, it was noted that the patient was more responsive and started to follow simple commands. His lab parameters were also showing an improvement in liver function with resolving coagulopathy and thrombocytopenia. With the dramatic improvement in mental status, transplant was placed on hold. His ventilator settings were weaned and the patient was extubated on day 12. TPE was discontinued after 12 daily sessions and CVVHDF was transitioned to intermittent hemodialysis.

He continued to have progressive recovery in liver and renal function. He was able to maintain an adequate urine volume and dialysis was discontinued. The patient was discharged after 29 days of hospitalization with complete recovery of his mental status and physical function. Six weeks after his initial injury, he had near-normal liver and kidney function and was to resume regular school activities (Table 1 and Fig. 1).

Discussion

In this case report, we demonstrate the benefit of prolonged CRRT in conjunction with TPE for the treatment of severe multiorgan failure secondary to heat stroke. Heat stroke is typically seen in previously healthy individuals undertaking strenuous exercise in a hot, humid environment and carries a mortality rate of up to 63 % [1, 2, 4]. Risk factors for the development of EHS include obesity, lack of acclimatization to environmental heat and humidity, and lack of physical fitness [3, 4], all of which were present in our patient.

Mechanisms of multiorgan dysfunction in EHS include the direct cytotoxicity of heat, an exaggerated acute phase response with increased production of inflammatory cytokines, decreased splanchnic blood flow with intestinal and hepatocellular hypoxia, and increased intestinal mucosal permeability with subsequent endotoxemia [5]. Another prominent feature in EHS is endothelial cell injury and microvascular thrombosis secondary to activation of coagulation and fibrinolysis [6]. While fibrinolysis may improve with treatment, coagulation activation continues, a similar pattern to that seen in sepsis [7, 8].

Mild to moderate hepatic injury is common in EHS, while fulminant hepatic failure has been reported in about 5 % of patients [9]. Obesity and subclinical non-alcoholic fatty liver may have contributed to the extremely morbid response to EHS observed in this patient. Orthotopic liver transplantation has been proposed to mitigate the morbidity and mortality of extensive liver damage [10]. However, a review of literature on liver transplant in heat stroke patients has not been encouraging [11]. Case reports showed that most died within a year of transplantation with only one long-term survivor [3, 11, 12].

An association between EHS and malignant hyperthermia (MH) has been proposed since cases of both entities have been associated with the presence of ryanodine receptor type 1 (RYR1) gene mutation or a positive caffeine halothane test [13]. Although a degree of overlap exists between EHS and other central core diseases, there is insufficient data to confirm a causal relationship at this time [14].

Thrombocytopenia-associated multiorgan failure (TAMOF) was the indication for instituting TPE in our patient. The pathophysiology underlying TAMOF has been postulated to include thrombotic microangiopathy [15]. Comparisons have been drawn to the low levels of ADAMTS-13 and the presence of ultra large von Willebrand factor (ULVWF), as seen in

Table 1 Laboratory parameters over the course of illness from admission to post-discharge

Laboratory parameters	Normal values	Day 1 admission	Day 3 prior to TPE	Day 8 TPE session #5	Post discharge
Hemoglobin (g/dl)	11–16	11.9	7.8	12.8	10.9
Hematocrit (%)	33–42	32.5	24.6	38.2	36.1
WBC (10^3/mm^3)	4.5–13	38.2	9.2	42.3	7.1
Platelets (10^3 per mm^3)	150–350×10^3	58	37	58	165
ADAMTS-13 (%)	56–253	46			
Glucose (mg/dl)	60–100	79	68	97	153
Creatinine (mg/dl)	0.3–0.7	1.10	3.40	2.14	1.3
Calcium(mg/dl)	8.0–11.0	7.6	9.7	11.2	11.2
Phosphorus (mg/dl)	3.4–5.2	6.4	6.2	3.1	4.2
Albumin (g/dl)	3.9–5.0	3.1	4.0	3.6	5.2
AST (U/l)	15–46	4388	7090	117	83
ALT (U/l)	21–72	2188	3868	118	70
Bilirubin, total (mg/dl)	0.2–1.3	2.9	17.6	23.4	1.2
Bilirubin, direct (mg/dl)	0.0 to 0.4	2.0	10.2	21.2	0.7
Ammonia (mmol/l)	21–50	<9	24	98	24
Lactic acid (mmol/l)	0.7–2.1	6.1	9.6	6.1	1.5
CPK (U/l)	56–433	4326	1186	459	29
PT (s)	10.1–12.6	60.1	52.9	29.4	15.3
PTT(s)	24.5–35.7	61.9	33.7	32.3	42.2
INR	1.0–2.0	2.8	3.15	2.53	1.23
Fibrinogen (mg/dl)	190–380	82	94	153	

WBC white blood cells, *ADAMTS-13* A disintegrin and metalloprotease with thrombospondin motifs-13, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CPK* creatine phosphokinase, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalized ratio

thrombotic thrombocytopenic purpura [16]. Plasma exchange was shown to have a significant beneficial treatment effect in sepsis-associated TAMOF as demonstrated by restoration of ADAMTS-13 activity, recovery of organ function, and reduction in mortality in a small single-center study in 2008 [15, 16]. We hypothesized that the benefits of plasma exchange seen in sepsis-associated thrombotic microangiopathy and TAMOF would be applicable to the endothelial injury and microvascular thrombosis seen in EHS [15, 17].

Therapeutic plasma exchange is an extracorporeal blood purification technique used to remove large molecular weight substances. It has been used as therapy in patients with liver failure of different etiologies, but there are only a few cases describing its use in multiorgan failure due to EHS [18–20]. Three previous studies that included pediatric patients have instituted plasma exchange in heat stroke under the theory that removal of inflammatory cytokines and myoglobin improves outcome [18–20]. In each of these reports,

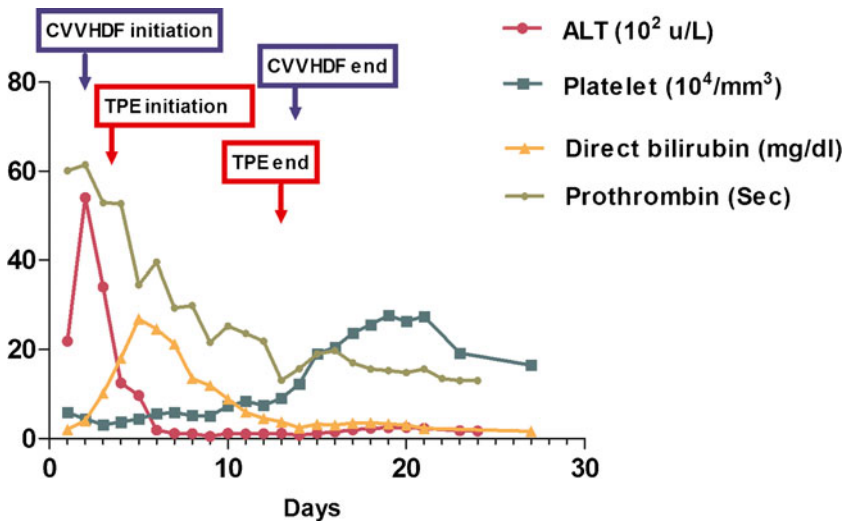

Fig. 1 Clinical course of heat stroke patient treated with prolonged continuous veno-venous hemodiafiltration (CVVHDF) and therapeutic plasma exchange (TPE). Change in laboratory parameters are graphed including liver function as alanine aminotransferase (ALT); direct bilirubinemia; bleeding disorders as platelets and prothrombin time

dramatic recovery followed the use of TPE. Similarly, our patient had full recovery of hepatic, neurological, and pulmonary function as well as remarkable recovery of renal function.

In summary, it is our opinion that patients with devastating multiorgan failure secondary to heat stroke may benefit greatly from the addition of TPE to other supportive measures. TPE should be instituted early in the course of the disease process, once there has been no significant improvement with conventional treatments. Recovery of organ function may require prolonged daily TPE. As seen in our patient, significant improvement was not clinically evident until the eighth session and we continued TPE for 12 sessions to solidify this recovery. Also, liver biopsy in this case may not have been the best prognostic indicator of potential hepatic recovery and, retrospectively, was insufficient justification for liver transplantation, which carries significant risks. Instead, the trend of the prothrombin activation, direct bilirubin, and ammonia levels were better markers of hepatic recovery. While further clinical trials and investigations are warranted, this case supports the potential use of TPE as supportive therapy in TAMOF secondary to EHS.

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