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ORIGINAL ARTICLE

The Liver Injury of Heat Stroke: A Systematic Review

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Abstract:
Heat stroke is a fatal disease caused by heat stress acting on the body. It is defined as severe heat stroke with core temperature >40℃ and central nervous system abnormality. Heat stroke disease is divided into two categories, namely exertional heat stroke and classical heat stroke. In this paper, the classification, definition, and diagnosis of heat stroke, and the pathogenesis, clinical manifestations and treatment progress of liver injury induced by heat stroke were summarized by referring to the recent domestic and foreign literature, and the existing problems that still need to be solved were put forward so as to provide new ideas for the study of liver injury induced by heat stroke.
Keywords: Heat stroke; Pathogenesis; liver injury; Clinical therapeutics

Background:

The heat stroke is a clinical disease with rapid progression characterized of body high temperature and multi-organ dysfunction .It has a high mortality rate and can be divided into exertional and classic heat stroke. Among them, exertional heat stroke is more common in healthy young people who are in physical labor, sports or military training. The disease progresses rapidly, the condition is critially. The onset of multiple organ failure, Treatment includes active fluid expanson, anti-infection and blood purification treatment. liver injury is one of the most serious complications of heat radiation disease. liver injury may lead to liver failure,which is one of the most important causes of death in patients. This review mainly describes the pathogenesis and treatment progress of liver injury in heat stroke.

Main text

I. International Classification Standards of Heat-Related Illness

According to international classification criteria, severe heat-related diseases include heat cramps, heat exhaustion and heat stroke, which have been used to assess the severity of heat-related diseases [1, 2]. Heat stroke can be divided into two categories of exertional heat stroke and classic heat stroke, and exertional heat stroke occurs most often in young and middle-aged people such as athletes, soldiers or heavy manual workers. Classic heat stroke mostly occurs in the elderly population, as well as in the high-risk population with complications such as obesity, diabetes, hypertension, heart disease, kidney disease, dementia and alcoholism.

According to the international classification standard, heat exhaustion can be defined as a mild-to-moderate fever caused by water or salt depletion in which core temperatures include those that may be normal, sub-normal, or slightly increased (more than 37◦C but less than 40◦C)[1]. The severe heat stroke with core body temperature (more than 40◦C) and central nervous system abnormalities can be often attributed to the scope of heat stroke. Therefore, according to the international classification, core body temperature is still one of the most important indicators to evaluate the severity of heat stroke. However, due to the influence of various factors, the core body temperature of patients with heat-related diseases may have begun to get below before they are transferred to another hospital [3, 4], which can cause the incident of misdiagnosis or **inappropriate treatment** to occur.

II. Classification of Heat Related Diseases That

Is Not Based on Body Temperature

The Japanese Association for Acute Medicine (JAAM) recently proposed a new classification system for the severity of heat related diseases that is not based on body temperature, so as to avoid underestimating the severity of the disease [5].

The system is mainly divided into three stages to assess the severity of the patient's condition. The first stage refers to the patient's presentation of any mild heat-related disease, including heat spasms and syncope. The patient's symptoms include dizziness, syncope, slight yawning, profuse sweating, muscle pain and muscle rigidity, and unconsciousness. The second stage means that the patient has any heat-related disease except the first stage or the third stage, and its signs and symptoms include headache, vomiting, fatigue, decreased attention, and impaired judgment. The third stage refers to patients with hyperthermia presenting severe heat-related disease under heat stress conditions, and the main manifestations of this stage are a neurological disorder, such as loss of consciousness and convulsions occurs. The results of blood bio-chemistry checking showed that there was dysfunction of liver, kidney or coagulation system.

III. Definition of Heat Stroke

So far, there is no unified definition of heatstroke that can be universally accepted. The most popular definition of heat stroke in the world is Bouchama's definition method of heat stroke, which defines heat stroke as the clinical manifestation after exposure to high temperature environment or intense exercise, accompanied by hot dry skin and central nervous system abnormalities, such as amentia, convulsion or coma, and with core body temperature of the patient exceeding 40 ° C. The researcher Pease and his partners cited the following criteria according to Bouchama's definition method of heat stroke: the patient's mental state disordered (including coma, delirium, disorientation or epilepsy); core body temperature > 40.6 ℃ or cooling evidence recorded before the first recorded temperature, the patient presents a history of thermal environment exposure and with hot dry skin.

Since 2006, the Japanese Association for Acute Medicine (JAAM) has collected data on patients diagnosed with high temperature related diseases (including heatstroke) through the nationwide high temperature related disease registration except the data of the core body temperature. In 2014, JAAM stipulated and published the standards for high-temperature related diseases including heat stroke [6].

IV. Diagnosis Standard of Heat Stroke

For various factors causing early changes of the heat stroke, the duration of high-temperature and the number of damaged organ within 72 hours after onset are independent risk factors and death related predictors. For the inclusion criteria and exclusion criteria, due to lacking of unified diagnostic criteria among medical centers, which results in the complexity of diagnostic terminology of heat strokes. In order to achieve the consistency and comparability of the data, the case review team referred to the newly recommended diagnostic (suspected) criteria in the Consensus of Experts on Diagnosis and Treatment of Heat Stroke in China. The established criteria are as follows: (1) Patients are exposed to high ambient temperature and / or high humidity environmental conditions to engage in high-intensity exercise, or are not exposed to high ambient temperature and / or high humidity environmental conditions to engage in high-intensity exercise; (2) The clinical manifestation mainly shows that the central nervous system function of the patient is impaired (for example, the patient presents with coma, convulsion, delirium, abnormal behavior and other symptoms); Core body temperature of the patient exceeds 40 ℃; Multiple organ function impairment (the number of damaged organs is greater than or equal to 2; and the damaged organs and tissue includes liver, kidney, gastrointestinal tract and striated muscle); Severe coagulation or disseminated intravascular coagulation disorders. In addition to any other clinical manifestations, if the patient's medical history information match with the true condition and the symptoms cannot be explained by other reasons, it is confirmed as heat stroke [7].

V. Pathogenesis of Liver Injury Induced by Heat Stroke

Systemic inflammatory response syndrome

(SIRS) is a key factor leading to multiple organ failure caused by heat stroke. liver function damage is often the first manifestation of heat stroke, and the severity of liver function damage also determines the severity of clinical symptoms and prognosis of patients. The causes of hepatocyte damage include dehydration secondary to ischemic liver injury and hypoperfusion caused by diverting blood from the visceral circulation to the skin to dissipate heat. At present, the pathogenesis of liver injury induced by heat stroke is still unclear. Research results show that factors such as mitochondrial apoptosis, mitochondrial autophagy, neutrophil extracellular trap networks, extracellular vesicles, and abnormal expression of heat shock proteins in liver cells all belong to the pathogenesis of liver injury induced by heat stroke.

5.1 Cell Apoptosis

Research on cell apoptosis has shown that in the rat model of acute liver injury caused by exertional heat shock, the main pathway of mitochondrial apoptosis and its related proteins are highly expressed in the liver tissue caused by exertional heat shock, while the expression of apoptosis-inhibiting proteins is low. Mitochondrial apoptosis plays an important role in acute liver injury caused by exertional heat radiation disease [8]. In acute liver injury caused by heat radiation disease, cytoplasmic p53 binds to Parkin and inhibits filamentous autophagy by preventing Parkin from translocating from the cytoplasm to mitochondria, thereby inhibiting the activation of filamentous autophagy and leading to hepatocyte apoptosis. In summary, inhibiting p53 may be a promising treatment for acute liver injury induced by heat stroke [9]. Some studies have shown that heat acceleration training (HAT) can mediate the liver mitochondrial autophagy process through the PINK1/Parkin-HIF-1a pathway, increase liver hypoperfusion tolerance, accelerate liver vascular endothelial repair,and thus play a protective role in liver [10].

5.2 Neutrophil Extracellular Traps

The neutral extracellar traps (NETs) are DNA-based reticular structures that are released from polymorphonuclear neutrophils into the extracellular space and are rich in multiple polymorphonuclear neutrophil-derived proteins such as mycoxidase (MPO), histones, and elastases, which plays a key role in impact on the pathogenesis of polymorphonuclear neutrophils. Animal experimental studies have confirmed that liver tissue during heat stroke is infiltrated by polymorphonuclear neutrophils, and the level of infiltration is positively correlated with the degree of liver injury. Therefore, it is speculated that it may be an important cause of acute liver injury, but the specific pathogenesis is unclear [11]. Some studies have shown that neutrophil extracellular trap may be activated by Nlrp3 inflammatory corpuscles/IL-1 β signal pathways, and mediate heat stress to cause induced liver injury [12], but the relevant pathogenesis remains to be further studied.

5.3 Extracellular Vesicles (EVS)

Extracellular vesicles (EVS) refer to membrane-enclosed vesicles secreted by mammals, and its elevated levels are related to pathological conditions such as inflammatory diseases, and are a new pathway for mediating intercellular communication [13]. Some studies have shown that extracellular vesicles derived from hepatocytes in heat stroke can induce apoptosis of hepatocytes, leading to liver injury [14].

5.4 Heat Shock Response (HSR)

Heat shock response (HSR) is a cellular defense mechanism against various external stresses, and its molecular basis is unclear. Some studies have shown that heat shock can induce different stress response signaling pathways and be triggered by different abnormal proteins [15]. Heat shock protein (HSP) is a large group of molecular chaperones found in most eukaryotes and bacteria, mainly responsible for the correct protein folding, protecting cells from stressors, and presenting immune and inflammatory cytokines; In addition, they are very important for regulating cell differentiation, survival, and death [16]. Among them, heat shock protein 70 (HSP70) in the heat shock protein family is a nonspecific protective protein that plays an important role in antioxidation, reducing stress damage, and protecting cells[17]. Soluble guanylate cyclase agonists can improve the survival rate of patients with heat stroke by increasing HSP70 [18]. The decreased expression of HSP70 in the serum of patients with exertional heat stroke is closely related to their prognosis, and can be used as a potential biological indicator for evaluating the

prognosis of exertional heat stroke [19], and the Pathogenesis of heat shock proteins in liver injury caused by heat stroke needs to be further studied.

5.5 Kupffer Cells

Kupffer cells are resident macrophages in the liver and are a major source of inflammatory cytokines. While macrophages are important chemokines, inflammatory protein-1α (mlip-1α) can aggravate the inflammatory response and secretion of Kupffer cells, including IL-6, TNF-α, IL-1β and inflammatory molecules. Studies have shown that decreased liver blood flow during intense exercise can lead to liver ischemia/hypoxia, and the activation of KUFFER cells in the liver can lead to the increase of free nitrogen and oxygen free radicals, lipid peroxidation and inflammation, resulting in increased release of IL-6 and TNF-a, and ultimately lead to liver cell injury. Significantly increased levels of IL-6 and TNF-a indicate that the rat model of exertion-type febrile disease can cause systemic inflammatory response syndrome and eventually lead to multiple organ failure [20].

Vi. Pathological Changes of Liver Injury

The results of hepatic laparoscopy in normal rats showed that there is a complete structure of hepatic lobules, and neatly arranged liver cells without inflammatory manifestations. The pathological characteristics of liver injury induced by heat stroke in rats are degeneration and necrosis of liver lobules. Hepatocyte swelling, hyperemia and edema, disordered arrangement, light cytoplasmic staining, inflammatory cell infiltration, and perinuclear vacuole formation were found in the rat model of exertional heat stroke. Massive hemorrhage and necrosis of cells in the central venous region were accompanied by hepatic sinuses congestion [21, 11].

VII. Clinical Manifestations of Liver Injury.

Liver injury is an important feature of exertional heat stroke. the most common clinical manifestations are fatigue, anorexia, scleral jaundice, hyperlacticacidemia, and even hypoglycemia. Liver injury is not only a common complication of heat stroke but also one of the important causes of death in patients with heatstroke [22]. After the occurrence of heat radiation disease, the blood flow in the liver decreased, complicated with DIC, and extensive microthrombus could be found in the liver, resulting in ischemia and hypoxia [23]. Symptoms of liver injury can be detected within hours of heat stroke, and it can rapidly develop into liver failure or even multiple-organ failure.

VIII. Auxiliary Inspection

The blood test results showed that the detection values of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase increased rapidly and reached a peak within 3 to 4 days (2 weeks in some patients). As the condition improves, the values of these indicators will gradually decrease. The elevation of bilirubin level is relatively delayed, and progressive jaundice usually begins to appear from 24 hours to 72 hours after the onset of heat stroke[24、25]. However, in the early stage of heat stroke, abdominal ultrasound and liver CT findings generally do not reveal significant abnormalities. Liver function examination can dynamically reflect the degree and changes of liver damage.

Ix. Judging Prognosis

If antipyretic drugs such as paracetamol are used to treat heatstroke at an early stage, the likelihood of developing liver failure will significantly increase [26,27,28]; The occurrence of thrombocytopenia in patients with acute liver failure is associated with the occurrence and poor prognosis of multiple organ failure. We speculate that the activation of platelets induced by systemic inflammatory reactions produces particles, leading to the removal of residual platelets and the reduction of platelets [29]; A key predictor of the progression of acute liver failure may be the presence of severe hypophosphatemia, which is particularly noteworthy in the context of impaired liver perfusion [30]. Possible pathogenesis of hypophosphatemia and acute liver failure include decreased adenosine triphosphate synthesis and decreased 2,3-diphosphoglycerate in red blood cells, leading to worsening liver oxygenation [31,32].

X. Treatment of Liver Injury Induced by Heat Stroke

"Cooling first, transportation second" is the principle of the treatment of thermal radiation disease. The optimal result of early induction cooling treatment is to reduce the patient's body temperature to below 38.9℃ within 30 minutes,

which is very critical. On this basis, various supportive treatments such as fluid replenishment are also very important for patients. Meanwhile, liver protection drug therapy and appropriate timing of blood purification treatment are also needed to improve the success rate of treatment. The symptoms of severe liver injury with heat shock, whether related to other organ dysfunction or not, can be improved by more than 80% by drug therapy alone. Impaired liver function can be improved even with very low prothrombin levels. Studies have shown that N-acetylcysteine can improve the survival rate of patients with heat-induced liver failure [33, 34], and it has been reported that it can be used to treat acute liver failure caused by heat stroke [35, 36, 37, 38].

Cases of liver failure caused by heat injection disease are very rare. At the same time, there is no established standard for liver transplantation at present, nor is there the best timing for preparation. The conservative treatment of heat injection disease in clinics is basic treatment, that is, rapid and effective lowering of the patient's body temperature. In a multicenter clinic study, Ichai and his partners found that the survival rate of patients after liver transplantation was higher [39], and many factors should be considered in liver transplantation, including patients' disease development dynamics, recovery status, and post-transplantation problems [40].

Conclusion:

There are still some problems to be solved about heat stroke: 1) there is no strong scientific evidence to support the use of core temperature threshold as an indicator to diagnose heat stroke; 2) More research is needed to demonstrate the molecular mechanism of liver injury induced by heat stroke; 3) Sensitive indicators for judging the severity of liver injury and related prognosis in heat stroke; 4) Drug treatment of liver injury induced by heat stroke; 5) Clinical criteria for liver transplantation due to liver injury induced by heat stroke.

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