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REVIEWARTICLE

HEPATIC MARKERS IN BURNS

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ABSTRACT

Burn injuries are of major concern with respect to morbidity and mortality.It isthe leading cause of death among children worldwide. Burn damages cell membrane, causes loss of cell integrity and membrane permeability which brings major changes in serum electrolytes. Liver, kidney and pancreas are among the most vulnerable organs in burn trauma, markers of which help to assess the pattern and severity of injury. Hepatic changes are constantly reported in burns. This includes plasma proteins, acute phase reactants, various enzymes and coagulation factors. These parameters suggest the degree of severity, risk involved and prognosis. This is an effort to put all these hepatic markers together.

INTRODUCTION

The liver has been shown to play a pivotal role after athermal injury (1, 2). After burn, the liver interacts with the site of injury and modulates the immune functions, the inflammatory processes, and the acute-phase response (1).Burns decrease protein and DNA concentrationof liver (1,3,4). Liver damage may be associated with increased hepatic edema formations which in turn lead to cell damage with the release of hepatic enzymes (2). In addition, fatty changes significantly increase during the first week after burn, peaked at 2 weeks after burn, and remain increased at 6, 9, and 12 months after burn (5,6).

Proteins and Burns

Aftera severe burn, hepatic protein synthesis shifts from constitutive proteins such as albumin, prealbumin, transferrin, and retinol-binding protein to acute phase proteins within 6 months (7-10).Total proteins and albumin were diminished also due to evaporation of water, hepatic dysfunction due to low perfusion(11). The hypoalbuminaemia, islargely due to exudation of albumin through the burn area but possibly also because of changes in the rates of synthesis and degradation. Levels of transferin also fall following burns (12) and due to the shorter half life of this protein (5 days compared with 20 days for albumin),this effect is seen earlier than with albumin. Recovery of circulating values also is more rapid. Retinol binding protein and thyroxine binding prealbumin, have even shorter half lives of about fifteen hours and 2.5 days respectively, blood levels fall even more rapidly, but tend to rise sooner in the healing phase (13). The finding that the rates of fall in circulating levels parallels the half lives of these four proteins supports the concept of greatly diminished protein synthesis soon after burn injury.In severe burn injury the saturation of transferrin is often low and thus transferrin levels cannot be taken as a guide to iron deficiency states. The assessment of iron status is more difficult by the large rises in ferritin levels in response to injury, with levels up to twenty times normal being found at the end of the first week following burn injury (12).Studies have shown that two mechanisms are responsible for the decrease of constitutive hepatic proteins:one is that the liver reprioritizes its protein synthesis from constitutive hepatic proteins to acute phase proteins. So the mRNA synthesis for constitutive hepatic proteins is decreased. The other reason is capillary leakage and the loss of proteins into the massive extravascular space and burn wound. Albumin and transferrin, however, have important physiologic functions as they serve as transporter proteins and contribute to osmotic pressure and plasma pH (14-17). Their down regulation after trauma has been described as potentially harmful and the synthesis of these proteins has been used as a predictor of mortality and indicators of recovery (17-22).

Hepatic Enzymes and Burns

Liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the most sensitive indicators of hepatocyte injury.Both the enzymes are normally present in low concentrations. Due to cellular injury or changes in cell membrane permeability, enzymes leak into circulation. Of the two, the ALT is the more sensitive and specific test for hepatocyte injury as AST also can be elevated in the state of myocardial infarction or muscle injury.The liver enzymes were significantly elevated during the first 3weeks after burn, normalizing over time. These findings are in agreement with

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those of another study inwhich the extent and the duration of the hepaticacute-phase response during the acute-phase post burn (23). An increase in edemaformation may lead to cell damage with the release of thehepatic enzymes (2). Liver enzymes, AST,ALT,ALP AND gamma GT are elevated because of impaired hepatic functions(11). Another study suggests that AST and ALT are increased and released into theserum for a period of 4 to 6 weeks, indicating that liver damage is present immediately after burn (23). Variations were reported in the pattern of alterations in hepatic enzymes. Serial measurements on admission showed a raise in AST, ALT by day 5. But the enzymes showed a fall in their levels by day 10. A constant elevation was seen in ALP and amylase through day 0 –day 10 (24).Severity of burn was assessed by percentage of total body surface area (TBSA) involved in the injury. A significant correlation was established between enzyme levels and burn size.

Serum glutamate dehydrogenasealso is a marker and is elevated in the state of severe hepatic damage.Serum alkaline phosphatase (ALP) provides an elevation of the patency of the bile channels at all levels, intrahepatic and extrahepatic. Serum levels are elevated in hepatobiliary disease. Elevation of creatine kinase (CK), hydroxybuturate dehydrogenase (HBD) and aspartate aminotransferase (AST) levels between the second and fourth days after injury are useful criteria in establishing the probability of electrical burn injury (25). In this study the enzyme levels found were many times greater than those anticipated for flame burns affecting a similar skin area, with CK levels sometimes 25 times the upper limit of normal. In patients with severe flame burns, however, lesser elevations of CK, ASAT and HBD may be found, and CK peak levels found on days 1-3 post burn in those with full-thickness burns presumably reflect local muscle damage.Serum bilirubinlevel was only increased for 2 weeks after burn, indicatingthat bilirubin level during the post burn response is not animportant marker as in other pathophysiological states, suchas sepsis. The intrahepaticcholestasis seemto be associated with an impairment of basolateral and canalicular hepatocyte transport of bile acids and organicanions (26). This is most likely caused by decreased transporterprotein and RNA expression. It has been shown that(26,27) decreased transporter expression isassociated with decreased bile acid output, leading toincreased intrahepatic bile concentration.

Acute phase Response to Burns

Liver damage has been associated with increased hepatocytecell death, which is caused by hepatocyte apoptosis and necrosis (1, 3, 6, 28, 29). Pathological studies found that10% to 15% of thermally injured patients have liver necrosisat autopsy. It has been also shown that a cutaneous thermal injuryalso induces liver cell apoptosis (1, 5, 30, 31). This increase inhepatic programmed cell death is compensated by an increase in hepatic cell proliferation, suggesting that the liver attemptsto maintain homeostasis (1). Severe burn is associated with increased cytokine levels in the serum and in the liver; Two possible mechanisms involved in the induction of hepatocyte apoptosisare hypoperfusion of thesplanchnic system and elevation of proinflammatorycytokines (4, 32). Acute-phase protein synthesisand metabolic impairment persists for almost 12 months, and the need for hepatic protein synthesis and metabolism leads toa massive liver enlargement. Burns produce a profound hyper metabolic stress response which is driven by the inflammatory response, which consists of cytokines, and acute phase proteins (18,19,33). Clinical studies have shown that increased hypermetabolic, inflammatory, and acute phase responses can be life threateningwith the uncontrolled and prolonged actionof counter regulatory stress hormones, proinflammatory cytokines (IL-1, IL-6, TNF-α), and acute phase proteins contributing to multiorgan failure, hyper metabolism, morbidity, and mortality (7,18,19). The acute phase response is a cascadeof events initiated to prevent tissue damage and to activate repair processes(7,9). The acute phase response is initiatedby activated phagocytic cells, fibroblasts and endothelial cells, which releaseproinflammatorycytokines leading to the systemic phase of theacute phase response (7,9). The liver synthesizes acute phase proteins; the bone marrow promotes further hemopoietic responses; and the immune system activates RES and the stimulation of lymphocytes (7,9). However,a crucial step in this cascade of reactions involves the interaction betweenthe site of injury and the liver, which isthe principle organ responsible for producing acute phase proteins and modulating the systemic inflammatory response.

The acute phase response usually encompasses positive acute phase proteins, whose expression is increased (C-reactive protein, α2-macroglobulin, haptoglobin, etc.) andnegative acute phase proteins, whoseexpression is decreased (albumin and prealbumin, transferrin, retinol-binding protein, etc). Immediately after burn, the damage of the liver maybe associated with an increased hepatic edema formation. It has been shown that the liver weight and liver/ bodyweight significantly increased 2 to 7 daysafter burn when compared with controls (34). Thermalinjury causes liver damage by edema formation, hypoperfusion, proinflammatory fragmentation, membrane blebbing, and phagocytosis of the apoptotic cell fragmentsby neighboring cells or extrusioninto the lumen of the bowel without inflammation.This is in contrast to necrosis, which involves cellular swelling, random DNA fragmentation, lysosomal activation,membrane breakdown, and extrusion ofcellular contents into the interstitium. Membrane breakdown and cellular content release induced inflammation withthe migration of inflammatory cells andrelease of pro - inflammatory cytokines andfree radicals, which leads to further tissue breakdown. Pathological studies found that 10% to 15% of thermally injured patients show signs of liver necrosis at autopsy(35). The necrosis is generally focal or zonal, central or paracentral, sometime smicrofocal, and related to burn shock and sepsis. The morphological differences betweenapoptosis and necrosis are used todifferentiate the two processes.A cutaneous thermal injury inducesliver cell apoptosis associated with caspaseactivation (34). This increasein hepatic programmed cell deathis compensated for by an increase in hepaticcell proliferation, suggesting that theliver attempts to maintain homeostasis. Despite the attempt to compensate increased apoptosis by increased hepatocyteproliferation, the liver cannot regain hepaticmass and protein concentration, aswe found a significant decrease in hepaticprotein concentration in burned rats. The mechanisms involved in a cutaneous burn inducing

programmed cell death in hepatocytes are not defined. Studies suggested that, in general, hypoperfusion and ischemia-reperfusion are associated to promote apoptosis (36–39). It can be surmisedthat the hepatic blood flow also decreases,thus causing programmed cell death. In addition, pro-inflammatory cytokines suchas IL-1 and tumor necrosis factor (TNF)-αhave been described to be an apoptoticsignal (40-44). After a thermal injury, serum and hepatic concentration of proinflammatorycytokines such as IL-1,IL-6, and TNF-αare increased (45–48). It is suggested thattwo possiblemechanisms are involved in increasedhepatocyte apoptosis: decreased splanchnicbloodflow; and elevation of pro-inflammatorycytokines, initiating intracellular signaling mechanisms. Signals that maybe involved encompass many signals that play an important role during the acute phase response.Previously, acute phase proteins were divided into type Iacute phase proteins, such as haptoglobinand α1-acidglycoprotein, mediated by IL-1-like cytokines (IL-1 and TNF) and type II acute phase proteins, such asα2-macroglobulin and fibrinogen, whichare mediated by IL-6 like cytokines (IL-6,IL-11) (7). It is unclear whether this divisionholds true with the discovery of new cytokines and signal transcription factors. Furthermore, it appears that there is a lot of cross-communication between the two responses, indicating that this strict division is not functional, and reflecting the ongoing responses. However,the up regulation of acute phase proteins represents a redirection of the liver to fulfill immune functions, metabolic responses, coagulation, and wound healing processes (7,9,49,50).

In contrast to acute phase proteins,constitutive hepatic proteins are down regulated (14-17). After a thermal injury, albumin and transferrin decrease by 50% to 70% below normal levels (14–17). Mediators of the acute phase response are cytokines. In several studies, the biphasic time course of proinflammatorycytokines has been demonstrated. Immediately after burn, IL-1, IL-6, IL-8, andTNF increase two- to ten-fold above normal levels, decrease slightly after approximately 12 hours, increase again,and then start to decrease. The authors concluded that the absence of IL-6 is an important determinant of hepatic dysfunction and mortality in sepsis, but more interesting is the fact that hepatic damage and dysfunction was associated with a three- to four-fold increase in mortality (51). Animal and human studies demonstrated that cytokines can either approach normal levels within 2 days after trauma or can be elevated up to 2 weeks after thermal injury (33,49-50,52-54). The signal transcription cascade includes various pro- and anti-inflammatory signal transcription factors (55-60).These signals activate transcription, translation, and expression of acute phase proteins. Particularly IL-6 has been speculated to be the main mediating cytokine. IL-6 activates glycoprotein 130 and the JAK-kinases (JAK-1) leading to activation of STAT 1 and 3 translocating to the nucleus. Intranuclear, the genes for acute phase proteins are turned on. The aim of the acute phaseresponse is to protect the body from further damage, and the aim will be achieved when all elements of the acute phase response coalesce in a balanced fashion. However, a prolonged increase in proinflammatory cytokines and acute phase proteins has been shown to be indicative of a hypercatabolic state, associated with an increased risk of sepsis, multiorgan failure, morbidity and mortality (61-62).

Coagulation and Clotting Factors in burns

Homeostasis of clotting is complex andhas been studied in thermally injured patients (63). Thrombotic and fibrinolytic mechanisms are activated after burn and the extent of activation isincreased with the severity of the thermal injury. Most homeostatic markers fall during the early phase of burns because of dilutional effects, loss, and degradation of plasma proteins. Clotting factors return to normal levels after the aggressive resuscitation period. Later in the post burn course, thrombogenicityhas been suggested to be increased due to fall inantithrombin III, protein C, and protein S levels while fibrinolysis activation occurs via increases in tissue plasminogen activation factor, thus leading to an increased risk of thrombosis. The hypercoagulable state places many thermally injured patients at risk for disseminated intravascular coagulation(DIC). Alterationsin clotting factors indicate liver damage and results in poor outcomes.The liver produces multiple coagulation factors which can be altered or become defective in liver injury. In the state of jaundice, vitamin K resorption is decreased, resulting in a decreased synthesis of prothrombin, or, when the liver is severely damaged or in a state of hepatocellulardysfunction, prothrombin is not synthesized at all. The diagnosis of pathological prothrombin synthesis is made by the prothrombin time (PT). PT as well as international normalized ratio (INR) are measures of the extrinsic pathway of coagualtion. Decreases in factors V, VII, IX and fibrinogen also have been noted in hepatic disease (64-65).

Conclusion

In summary, liver is one of the most important organs that is affected in thermal injury. It plays an important role in morbidity and mortality. Enzymes, plasma protein levels and acute phase reactants act as markers of prognostication in burns. Restoration of liver functions has a pivotal role in the survival of the patients.

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