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Serum Markers Associated With Traumatic Patients- a Review Article

KEYWORDS

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Introduction-
There are many immunological alterations that occur after trauma which may cause the multiple organ dysfunction syndrome (MODS) and death. Early evaluation of the prognosis in traumatised patients is difficult. Traditionally, the clinical condition and management of the patient are assessed by evaluation of cardiovascular, renal, liver and respiratory functions. Nevertheless, the significance of such clinical parameters as the urinary output, oxygen saturation, blood gases, C-reactive protein, base excess, etc, is limited since only patients with a clearly impaired organ function can be distinguished. As a result of the popularity of the microenvironment theory and the availability of techniques to measure molecular mediators, studies have been undertaken to search for inflammatory markers which could detect patients in the 'borderline condition' and at risk of developing post-traumatic complications.Alteration of treatment may then prevent the onset of adverse sequelae. The purpose of this review is to highlight our current knowledge on the effectiveness of the existing inflammatory markers of immune reactivity and evaluate their impact on our clinical practice.

Lipopolysaccharaide-binding protein (LBP). This is a 58kDa class-I acute-phase protein of mainly hepatic origin with the ability to bind bacterial lipopolysaccharide (LPS).22 LPSactivatedmacrophages release proinflammatory cytokines, such as IL-6, IL-1 and tumour-necrosis-factor (TNF). LPB is synthesised in hepatocytes and released into the blood. During the acute-phase response, this synthesis and release can increase up to 30-fold.22 LBP was found to block the effects of LPS *in vitro* and protect mice from lethal outcome.23 LPS-induced production of cytokines by macrophages was decreased by high concentrations of LBP.Increased levels of LBP also prevented liver injury and reduced mortality after an injection of LPS in mice. However, low concentrations of LPB enhanced production of TN in macrophages induced by LPS. In general terms, LBP enhances the effects of LPS when it is present in smallquantities, whereas it suppresses them in high concentrations. Levels of LBP rise in patients during the acute phase of trauma or sepsis, with maximum values occurring on the second and third days. In patients with MODS significantly higher concentrations of LBP were found in those with documented infection. By contrast, no significant differences were found between patients with SIRS and the non-septic MODS group, suggesting that LBP may be used as a marker to differentiate between SIRS and ongoing bacterial sepsis in the early post-traumatic course. In patients with severe sepsis or septic shock, concentrations of LBP were found to be significantly increased and it may have prognostic significance in such patients.

C-reactive protein (CRP)- This is one of the acute-phase response proteins produced by hepatocytes and is usually found in concentrations of 0.3 to 1.7 mg/1.28 Increased production is due to cytokine-dependent induction of synthesis and elevated levels may be detected within eight hours of a stimulus and can reach 500 mg/1.28 Besides trauma, elevated levels of CRP may be seen in other conditions such as autoimmune disease, infection and malignancy. The level of CRP normally peaks within 48 hours of the stimulus. A fall in serial measurements usually indicates resolution of the underlying process, while persisting elevated levels may indicate ongoing inflammation or infection. CRP is not considered to be an ideal marker of the inflammatory mediator response after trauma.

Procalcitonin (PCT). This is derived from a precursor protein preprocalcitonin, proteolysis of which results in the formation of calcitonin. The latter is normally produced in the C-cells of the thyroid. PCT is not normally detected in the plasma of healthy individuals. A study of hepatocyte tissue culture treated with TNF-a or IL-6 has shown detectable levels of PCT after 24 hours of culture, suggesting that the liver is a potential source of production of PCT. In polytraumatised patients injury leads to increased plasma levels of PTC dependent on the severity of injury, with peak values on the first and third days. Increased concentrations of PCT during the first days after trauma have been shown to predict severe SIRS, sepsis and MODS. Thus, PCT may be a useful marker for monitoring the inflammatory status in these patients.

Tumour necrosis factor (TNF). This is an autocoid which exists in multimers of two or three identical subunits and contains several potential sites of glycosylation. TNF and TNF may be distinguished. Both have almost the same biological effects. TNF is only synthesised by lymphocytes. In inflammatory reactions, TNF is mainly involved. It may also exist as an integral membrane protein TNF is a central regulator in the immunoinflammatory response after trauma and is produced by monocytes, lymphocytes, Kupffer cells, macrophages, endothelial cells and glial cells. Most of the available studies of TNF on patients with multiple injuries have been focused on the clinical course of patients in intensive-care units. Despite the initiation of treatment continually high levels of TNF have been reported to correlate with a poor outcome, although there was no significant difference in the levels of TNF when study commenced.

Interleukin-1 (IL-1). This family of peptides consists of three structurally related polypeptides: IL-1 and IL-1 receptor antagonist (IL-1ra), produced primarily by monocytes. It

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is primarily induced in the presence of ischaemia or sepsis by activated macrophages and activated endothelial cells. Biologically, IL-1 has a similar activity to that of TNF and acts synergistically with it with induction of fever, hypotension, endothelial cell adhesion as a procoagulant, and the chemotaxis of polymorphonuclear leucocytes (PMNs) and macrophages. In addition, IL-1 induces release of TNF, IL-6, IL-8, platelet activating factor (PAF) and eicosanoids.52 The circulating half-life of IL-1 is six minutes. This makes its detection after injury much less likely than that of TNF-á. Most studies carried out to assess the efficacy of this marker have been done in septic patients in whom it was found that the levels of IL-1 did not correlate with death or MODS.

phage-deactivation factor. It decreases cytokine production of Th1 cells, which synthesise IL-2, IL-3, IFN and TNF. These cells induce a type-IV immune reaction, a delayed type of hypersensitivity reaction (DTH), via cytotoxic T-cells while cytokines of the Th2 clone cause a humoral immune response. Moreover, IL-10 inhibits both the antigen- presenting function of macrophages and the subsequent proliferation of T-cells. The plasma concentrations of IL-10 are elevated in patients with polytrauma and after major surgery and a correlation with the severity of the injury has been reported.An increased plasma concentrations of IL-10 has been observed in septic patients and even higher values have been found in patients who had suffered septic shock. However, other studies have shown an unchanged secretion of IL-10 in patients undergoing major surgical procedures and even depressed concentrations in trauma patients.

Cytokines-Cytokines exert their effects by interaction with receptor systems and mediate intercellular events which often involve transcription of DNA. The effect of TNF is mediated by the binding to two membrane-bound receptors (TNF-RI, 55kD and TNF-RII, 75kD), which are found on nearly all cell types. In polytraumatised patients, increased concentrations of membrane bound receptors were found to correlate with increased rates of MODS.

Adhesion molecules. The adhesion of polymorphonuclear leucocytes (PMNs) to capillary endothelial cells is the decisive step for their migration to the site of inflammation and the hallmark of the 'microenvironment theory'. The adhesion is provided by adhesion molecules, which are present both on the PMN and on the surface of endothelial cells. Three major groups of adhesion molecule are distinguished: selectins, immune globulins and integrines. Bothselectins and immune globulins also appear in a soluble form (sEselectin and sICAM-1). All these proteins provide a specific attachment between the ligand and the receptor, so that a selective accumulation of PMNs occurs in the inflammatory tissue. The soluble form of L-selectin (s-L-selectin) can be detected in blood serum. s-PMN-bound L-selectin was significantly reduced in deceased septic patients and in trauma patients with posttraumatic MODS.levels of soluble Eselectin and soluble ICAM-1 were found to be significantly raised in the plasma by the third day after injury, the magnitude of the increase being related to the degree of injury. Law et al112 reported a significant correlation between the elevated levels of soluble ICAM-1 and the later occurrence and severity of MODS.

Conclusion

Understanding of the pathophysiology and the immunobiology of both traumatic and surgical injury have contributed considerably to the debate surrounding the aetiology of post-traumatic complications. Trauma and shock lead to an activation of multiple humoral and cellular cascade mechanisms, such as inflammatory mediators, as well as complex mechanisms of host defence. These immune logical defence mechanisms may become insufficient and allow further omplications. Generalised capillary damage, increase in permeability, and subsequent multiple organ dysfunction or failure belong to the clinical picture of MODS. Despite the application of conventional and supportive treatment in the intensive-care unit, the clinical results in patients with ARDS and MODS remain disappointing.

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