REVIEW

The Effect of Head Injury Upon the Immune System

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Abstract

Severe head injuries are characterized by high mortality and morbidity. In spite of guidelines based therapy the treatment is frequently unsuccessful. Extracranial infectious complications are considered to be an important problem during the course of recovery, and possibly immunological changes could explain their occurrence. Head injuries cause an imbalance within the helper cell community, resulting in a $T_{h2}$ dominance. This development is influenced by the soluble agents of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. The crucial research of damaged cellular immunity concluded Quattrocchi in 1991. Both the activation of microglial cells and the accumulation of T-cells after crossing the BBB indicate production of pro-inflammatory mediators in the CNS after injury. The leaking of pro-inflammatory mediators to the circulation develops to a systemic inflammatory response syndrome (SIRS). On the contrary, an overwhelming of anti-inflammatory substances leads to an anti-inflammatory response syndrome (CARS). It is suggested that an imbalance between these two immune responses is responsible for organ dysfunction and increased susceptibility to infections in polytrauma victims. Concerning mediators, IL-6 draws attention because of its high marker ability. Finally, post-traumatic infections have also been correlated with an altered function of antigen-presenting cells (APC). Concerning the quantity, the humoral part of immune system seems to be stimulated, but its function and phagocyte activity shows several defects. Finally, $T_{h2}$ dominance induces IgE levels accumulation. All these changes are strongly under effect of stress based release of endogenous glucocorticoids and catecholamine, which influence the complex network of cytokines and cell mediators (Fig. 3, Ref. 18). Full Text (Free, PDF) www.bmj.sk.

Key words: severe head injuries, immune system, stress reaction, $T_{h2}$ dominance.

Head injuries are the third most common pathology in the central nervous system and it counts for a main cause of mortality and disability among people between the age of 20 and 40. This group has a major representation of male victims. Head injuries can be divided by many points of view. In compliance with our research it is apposite to divide them into two groups – primary and secondary lesions. Studying polytrauma mortality generally, it is shown that deaths occurring immediately or early after the trauma is determined by primary brain injuries or hemorrhagic shock. Deaths occurring later after hospitalization are due to secondary brain injuries or host defense failure (reversible systemic inflammation) (1). These indications further highlight the clinical importance of head trauma.

Brain injury serves as one of the most challenging problems facing clinicians. A quick pre- and in-hospital management is of great importance for the outcome of the patient and has during recent decades been brought to light. This has improved the chances of a positive outcome and thus lowered the mortality rate significantly (2, 3). Still, understanding of the pathophysiology behind the brain injury and its consequences becomes the theoretical basis that enhances the possibility of a better and more effective therapeutic treatment.

The goal of the successful therapy is to protect the brain from secondary insults keeping CPP level above 60. In spite of guidelines based therapy the mortality of brain injuries is high. How-

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ever, recent decades of research has illuminated other independent factors, which indeed influence the outcome. Particularly extra cranial infectious complications are considered an important problem during the course of recovery, and it has been suggested that immunological changes could explain their occurrence. Immune system and its changes are well regulated by complex network of neuro-immune cross talk, issuing highly specific regulatory control. Changes in different parts of the host defense mechanisms could supposedly influence the outcome by making way for extra cranial complications. Many studies have evaluated these effects of head injury, and especially the cellular arm reports significant differences in comparison with the non injured person. It is indicated that patients surviving their trauma will have a full recovery and normalization of their immune system (4).

On the other hand, the more detailed nature of the immunological changes has not yet been sufficiently investigated. Although, many speculators agree on the theory that head injury causes most likely an imbalance within the TH (helper) cell community, resulting in a $T_{h2}$ dominance. This development is clearly influenced by the soluble agents of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.

A $T_{h2}$ dependent response suppresses the cellular immunity and instead stimulates the humoral parts. Probably this has evolved to protect the host from an overwhelming of potentially harmful inflammatory mediators. However, it seems as if these events also increase the patient’s susceptibility for developing an infection.

**History**

In 1991 Quattrocchi et al (5) reported suppression of multiple parameters of cellular immune function along with a higher incidence of infection. In vivo observations of delayed type hypersensitivity (DTH) skin anergy were noticed, but even more interesting in vitro changes occurred. When stimulated with lymphocyte mitogen, phytohaemagglutinin (PHA), the peripheral blood lymphocytes obtained within 24 hour after injury showed impaired phenotypic expression of CD2+$^+$ (T-cell), CD4+$^+$ (T-helper-cell) and CD25+$^+$ (alpha subunit of the interleukin-2 receptor). Also a decreased blastogenesis was observed. This highly suggests head injury to alter the helper T-cells ability to answer to mitogen stimulation and thus suppress their activity. Quattrocchi et al (5) discuss this to be due to presence of suppressor cells, soluble mediators or intrinsic T-cell dysfunction.

These hypothesis became the subject of their next publication, Quattrocchi et al (6). In addition to their early material they now presented data from other studies showing suppression of IL-2 and INF-gamma production (without changes in IL-1 production) and also suppression of LAK (lymphokine-activated killer) cytotoxicity (CD8+$^+$ T-cells). This indicates a general decreased function of both CD8+$^+$ and CD4+$^+$ effectors T-cells. In their own experiments they could confirm the influence of suppressor lymphocytes and also postulated the rapidity of immune suppression to be due to significant effects of soluble serum factors. Since these studies many more have followed showing more or less the same results. Meert et al (7) repeated the similar
investigations as Quattrocchi et al had preformed some years earlier, but this time in children between the ages of 17 to 18 suffering from severe head injury. The results showed to be comparable, with marked suppression in T-lymphocyte circulating numbers, activation and mitogenesis, within the first two weeks after trauma. Wolach et al (4), showed significant deficiencies of all lymphocyte phenotypes of the cellular arm (CD4+, CD8+ and circulating T-cells) and also NK-cells, in comatose patients after severe brain injury.

**Systemic consequences of trauma**

Both the activation of microglial cells and the accumulation of T-cells after crossing the BBB indicate production of pro-inflammatory mediators in the CNS after injury. The leaking of pro-inflammatory mediators to the circulation develops to type of hyperinflammation referred to as **systemic inflammatory response syndrome** (SIRS) (Fig. 1). On the contrary, an overwhelming of anti-inflammatory substances leads to a systemic hypo-inflammation known as compensatory **anti-inflammatory response syndrome** (CARS) (Fig. 2). It is suggested that an imbalance between these two immune responses is responsible for organ dysfunction and increased susceptibility to infections observed in polytrauma victims. Keel et al (1) present neurons, glial cells and astrocytes as producers of both pro- and anti-inflammatory substances and their receptors, resulting in local inflammation and leakage to the circulation with a following SIRS. The local inflammation in the CNS does not differ much from other tissue inflammatory responses after injury, and the same both protective and harming effects are observed (8). Studying the cytokines after brain injury confirms this suggestion. Lau et al (9) found in vitro that astrocytes produce and release interleukin 1, interleukin 6, tumor necrosis factor alpha and interferon gamma 1 hour after shear stress. Further research confirms these results and especially IL-6 draws attention, because it seems to be a good marker for the severity of brain injury. Indeed, IL-6 is well known to induce release and production of acute phase proteins in hepatocytes. This would explain the existents of an acute phase response in close head injured patient, observed by Young et al (10). Woiciechowsky et al (11) confirmed this raise in IL-6 levels, but could also correlate the plasma concentrations of IL-6 with the severity of brain injury and pneumonia, thus proposing an influence of head injury on the occurring of post-trauma infections. This mediator is produced by many cells and acts on most cells, but only stimulating effects have been observed. For example, IL-6 can together with IL-1 function as a co-stimulatory signal in T-cell activation, but its most important effect has showed to be stimulating B-cells to differentiate into plasma cells (1).

Decreased resistance to infection is observed in patients with serious traumatic injury and major burns. Suppression of cell-mediated immunity is known to occur in these patients and several detailed investigations have explored its regulatory nature.

Concerning T-helper cells (TH), O’Sullivan et al (12) found the impaired adaptive immunity not only to be a generalized suppression, but rather a conversion of the naive TH cells towards the \( T_{h2} \) phenotype. Thus, although the mean T-lymphocyte levels may be decreased, the \( T_{h1}/T_{h2} \) ratio is changed leading to a raised concentration \( T_{h2} \), compared with the non traumatic patient (Fig. 3). This is supported by reduced serum concentrations of IL-2 and IL-12, along with a major increase in IL-4 and IL-10. Several recent studies show similar results and also report elevated serum levels of IL-13 and transforming growth factor-\( \beta \) (TGF-\( \beta \)), produced by both \( T_{h2} \) cells and monocytes/macrophages (13). Although the anti-inflammatory effect of IL-4 is of great interest considering the aspects of suppressed immunity in head injured patients, we must not forget to mention the pro-inflammatory properties. In naive B-cells, IL-4 is well known to induce heavy chain isotype switching, proliferation and differentiation into plasma-cells, leading to an increased production of immunoglobulin E (14). Summarizing these events, it seems as if severe traumatic injury and burns is followed by an increased production of IL-10, IL-13 and IL-4 by \( T_{h2} \) cells and mono-

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**Fig. 2.** Traumatic injury results in a TH2 type response and a depressed expression of MHC class II. These events will suppress several aspects of the immune responsiveness, further increasing the susceptibility of post-traumatic infectious complication. (Picture redrawn and modified from Keel M et al, 2005.)
cytes/macrophages, leading to a decreased resistance to infection correlating with subsequent septic events (Fig. 2). If closed head injury affects the immunological events similarly is yet to be proved. Finally, post-traumatic infections also have been correlated with an altered function of antigen-presenting cells (APC). These, mainly monocytes/macrophages, show reduced expression of co-stimulators and the MHC (major histocompatibility complex) class II molecule HLA-DR (human leukocyte antigen) (13).

Aspects of humoral and phagocyte functions after severe isolated head injury

Humoral and phagocyte functions involve immunoglobulins, complement components, monocytes/macrophages and polymorph nuclear leucocytes (PMNL).

There are not many studies available focusing on these parameters after severe head injury, mainly because no major effects have been noticed to occur. However, Wolach et al (4, 14) included major investigations of the phagocyte and humoral functions in their observations of immunological defects in comatose patients after severe head injury. All investigations were made in peripheral blood.

Starting with the phagocyte arm, they observed a reduced generation of superoxide by neutrophils when in vitro stimulated with formyl-methionyl-leucyl-proline (fMLP) and phorbolmyristate acetate (PMA). The authors referred to former studies showing that PMNLs become hyperactive during the first 12 hours of the post-traumatic period, thereafter, entering a late phase where they reduce in number and function up till 72 hours after trauma. The effects are believed to be caused by changes in concentrations of pro-inflammatory mediators. Wolach et al showed similar results in head injured patients, both in their study 1993 (14) and 2001 (4).

Abnormal humoral function could explain the defective bacterial activity of the PMNLs. Adding homologous serum in vitro corrected the PMNL impairment, indicating deficient opsonisation, an essential precondition for phagocytosis. As shown in the paper from 1993 (14), neither superoxide anion release nor random migration or chemotactic capability was defective in the neutrophils, confirming the theory of a defect humoral function.

Early reduction in complement components Clq, C1r and C4, along with deficiencies of IgG2 and IgG4 seems to be the reason. These levels increase quickly after head injury and stay normal during the vegetative period. Since the number of B-cells show post-traumatic changes, the decrease is supposed to be caused by increased consumption of the mediators. The time courses of all these events well correlates with the changes observed in PMNL function, thus confirming the early and late period hypothesis, also known as the two-hit model. Observations of high IgE levels after trauma and cerebral infarction are mentioned in a few studies, suggesting a post-traumatic conversion of the T_{h1}-cells towards the T_{h2} phenotype (15).

The changes in cytokine concentrations after trauma are in most aspects quite well studied, but still the mechanisms behind the observed alterations are not very clear. Elenkov et al (16, 17, 18) have during the last ten years published data suggesting that the stress-induced glucocorticoids and catecholamine strongly affect the balance between T_{h1} and T_{h2}. If true, this would add valuable facts to the understanding of immune alterations after head injury.

In 1996 (16), they reported alterations to occur in the cytokine panorama produced by cells in response to bacterial lipopolysaccharide (LPS) in human whole blood, when exposed to the known mediators of stress. Glucocorticoids showed to strongly decrease the serum levels of IL-12, the well known inducer of T_{h1} phenotypic differentiation. Catecholamines showed the same results; however, they also increased the serum concentrations of IL-10. The effects are mediated through both APC and the lymphocytes themselves. These observations suggest a highly selective suppression of T_{h1} function and a shift toward T_{h2} cytokine pattern in response to stressful stimulation. Hence,
this could explain some very important CNS regulatory pathways of immune function, and also influence the susceptibility of an individual to certain infectious diseases after trauma.

Similar observations were made in 2000 (17), but now serum levels of histamine and adenosine seemed to have similar effects as glucocorticoids and catecholamine. Except IL-12, other Tα-1 stimulating signal molecules, such as TNF-β, INF-α and INF-gamma, showed to suffer the same suppression. Summarizing all their observations in the review from 2004 (18), Elenkov et al reported the last evidence for an up-regulation of IL-4, IL-6 and IL-13 levels after stress reaction, once again confirming their hypothesis. It is important to note that all these effects are seen in vivo after endogenous changes in different mediator concentrations, everything within the physiological range.

Conclusions

The effects of severe closed head injury upon the immune system are mainly issued through impairment of the cellular aspects. Trauma is directly followed by a decreased number of circulating T-lymphocytes, helper cells imbalance and impaired T-lymphocyte activation and proliferation. Also decreased numbers of NK-cells are described. The most presumptive reason could be an early reduction in complement components Clq, C1r and C4, along with deficiencies of IgG2 and IgG4. Finally Tα2 dominance induces IgE levels accumulation reaching the values typical for atopic reaction or parasitic disease.

Phagocyte impairment of the PMNL ability to kill bacteria is correlated with defective opsonisation, probably due to increased consumption of humoral mediators early after trauma. After initial deficiency, the humoral immunity shows a quick recovery in most patients, except from increased concentrations of IgE. All these changes are strongly under effect of stress based release of endogenous glucocorticoids and catecholamine, which influence the complex network of cytokines and cell mediators.

Whether head injuries affect the immune system or not, seems quite obvious. That this modulation increases the risk for developing extracranial infectious complications, has also found strong evidence. However, the detailed nature of the host defense mechanism and its regulation, during the posttraumatic period is still to be revealed. So far, we can only speculate, but several indications suggest a highly controlled cross talk of events, rather than just mere accidental suppression. Learning more about these connections will bring us closer to the full understanding of their purposes, and might even create modern approaches for future therapies.

Although many of the concerns in the concept of neuro-immune cross talk, and particularly its alterations after head injury, is suggested, there are still many problems to be solved and hypothesis to be proved. However, it is still clear that a connection exists and that modulated change of the immune system does appear after head trauma.

References


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