Cell-mediated immunity in severely head-injured patients: the role of suppressor lymphocytes and serum factors

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Severe head injury results in suppression of cellular immunity associated with defective in vitro functioning of effector lymphocytes, such as helper T cells and cytotoxic T cells. It is not known whether this suppression in effector lymphocyte function is due to intrinsic lymphocyte dysfunction, to suppressor peripheral blood mononuclear cells (PBMC's) such as suppressor lymphocytes or suppressor monocytes, or to serum factors capable of inhibiting effector lymphocyte function. The purpose of this study was to determine whether a subpopulation of PBMC's and/or serum factor(s) are responsible for this observed suppression in cell-mediated immunity.

Cell-mediated immune activity was determined measuring in vitro lymphokine-activated killer (LAK) cytotoxicity following incubation of PBMC's from 15 head-injured patients with those from 15 heterologous normal subjects. The PBMC's were separated into lymphocyte-enriched and monocyte-enriched subpopulations by plastic adherence techniques, and the effect of each population on LAK cytotoxicity was determined. Additionally, the effect on cytotoxicity of serum from the head-injured patients was determined in a dose-response fashion.

There was significant depression in LAK cytotoxicity when: 1) PBMC's from normal subjects were incubated with PBMC's from head-injured patients (p < 0.001); 2) lymphocytes (PBMC's depleted of monocytes) from head-injured patients were incubated with PBMC's from normal subjects (p < 0.001); and 3) PBMC's from normal subjects were incubated with serum from head-injured patients (p < 0.001). No suppression in cellular immunity was noted when lymphocytes from normal subjects were incubated with monocytes from head-injured patients.

The results indicate that lymphocytes rather than monocytes actively inhibit cellular immunity following severe head injury. The detection of immunosuppressive serum factors suggests a mechanism by which lymphocytes might be modulated by severe head injury.

KEY WORDS  •  head injury  •  infection  •  lymphokine-activated killer cell  •  immunocompetence

RECENT investigations indicate that severe head injury, even in the absence of systemic injury, results in suppression of cellular immune function. Parameters of in vivo and in vitro cellular immune function found to be suppressed following isolated severe head injury in man include: 1) delayed-type hypersensitivity skin test responses; 2) in vitro phytohemagglutinin (PHA)-stimulated helper T cell activation; 3) in vitro PHA-stimulated interleukin-2 (IL-2) and interferon-γ (INF-γ) production; and 4) in vitro lymphokine-activated killer (LAK) cytotoxicity. These studies suggest that the function of effector lymphocytes, such as helper T cells and cytotoxic T cells, is suppressed following isolated severe head injury. It is not clear, however, whether this suppression is due to intrinsic defects in effector lymphocyte activity, active suppression of effector lymphocytes by suppressor lymphocytes or suppressor monocytes, or serum factors capable of suppressing effector lymphocyte function.

The purpose of this study was to determine whether isolated severe head injury is associated with a specific subset of peripheral blood mononuclear cells (PBMC's) capable of inhibiting effector lymphocyte function and whether immunosuppressive serum factors are present. In order to determine whether PBMC's from head-
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injured patients can actively inhibit cellular immune function, we investigated the effect of incubating PBMC’s from normal subjects with PBMC’s from head-injured patients on LAK cytotoxicity, an in vitro measure of cellular immune activity. The possible contribution of the lymphocyte and monocyte subpopulations of PBMC’s to this suppression of effector lymphocyte function was determined by separating PBMC’s from head-injured patients into lymphocyte-enriched and monocyte-enriched fractions, utilizing plastic adherence techniques, and determining the effect of each fraction of LAK cytotoxicity. Additionally, the dose-response effect of serum from head-injured patients on in vitro LAK cytotoxicity was evaluated to determine whether soluble inhibitory mediators were present.

Materials and Methods

Clinical Material

From January 1 through June 30, 1991, 11 male and four female patients (mean age 23 years, range 17 to 49 years) with isolated severe head injury were prospectively selected for evaluation. Ten healthy male and five healthy female subjects were selected as controls (mean age 27 years, range 20 to 44 years). The criterion for enrollment in the study was an admission Glasgow Coma Scale score of less than 9 following severe head injury. Patients with significant systemic injury, defined by an Injury Severity Scale score of greater than 27, were excluded. In addition, patients treated with blood transfusions and corticosteroids, as well as those with postruama hypotension, hypoxia, or spinal cord injury were excluded. On admission, all patients were intubated for hyperventilation: nine received a mannitol intravenous loading dose (0.5 gm/kg) and 11 received a phenytoin intravenous loading dose (15 mg/kg). Table 1 summarizes the admission and treatment data.

Isolation and Incubation of PBMC’s

The PBMC’s were isolated as described by Miller and Levy.2 Briefly, peripheral venous blood was collected within 24 hours after injury, and PBMC’s were obtained by density centrifugation. The mononuclear layer was harvested, washed in phosphate-buffered saline, and adjusted to 5 × 10⁶ cells/ml in culture medium (CM), which consisted of RPMI 1640 with 15% fetal calf serum, 25 mM HEPES buffer, 1 mM L-glutamine, and 100 U/ml of penicillin with 100 µg/ml of streptomycin.* Viability was determined by trypan blue dye exclusion.

Fractionation of PBMC’s Into Lymphocyte and Monocyte Subpopulations

We separated PBMC’s into lymphocyte and monocyte subpopulations as described by Vercelli, et al.37

Essentially, PBMC’s at a concentration of 5 × 10⁶ cells/ml were incubated for 2 hour at 37°C in plastic Petri dishes. The nonadherent fraction was then removed by gently washing with CM. After removal of the nonadherent layer, the dishes were scraped with a rubber spatula and the cells resuspended with CM. Cytocentrifuged preparations, stained with Wright-Giemsa and nonspecific esterase, revealed that the adherent cells contained more than 95% monocytes, whereas the nonadherent cells contained more than 95% lymphocytes. The nonadherent lymphocyte-enriched population will be termed “lymphocytes,” whereas the adherent monocyte-enriched population will be termed “monocytes.” Prior to incubation, lymphocytes were adjusted to 5 × 10⁵ cells/ml in CM, whereas monocytes were adjusted to 5 × 10⁵ cells/ml. Viability was determined by trypan blue dye exclusion (always > 95%).

Incubation of PBMC’s From Head-Injured Patients With PBMC’s From Normal Subjects

The PBMC’s from 15 head-injured patients were incubated with heterologous PBMC’s from 15 normal subjects. In each experiment 1 ml of PBMC’s (5 × 10⁶ cells/ml) from one head-injured patient was incubated with 1 ml of PBMC’s (5 × 10⁶ cells/ml) from one normal subject. Cells were incubated for 72 hours at 37°C in 5% CO₂ with 500 U/ml of recombinant IL-2. Controls consisted of PBMC’s from 15 normal subjects incubated with PBMC’s from 15 heterologous normal subjects. Following incubation, cell viability was assessed.

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* Table 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Finding</th>
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<tbody>
<tr>
<td>age (yrs)</td>
<td>23</td>
</tr>
<tr>
<td>mean range</td>
<td>17-49</td>
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<tr>
<td>admission GCS mean</td>
<td>7</td>
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<tr>
<td>mean range</td>
<td>4-8</td>
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<tr>
<td>mode of injury</td>
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<tr>
<td>motor-vehicle accident</td>
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<tr>
<td>gunshot wound</td>
<td>20%</td>
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<tr>
<td>admission CT finding</td>
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<tr>
<td>epidural hematoma</td>
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<tr>
<td>cerebral contusion</td>
<td>13%</td>
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<td>intracerebral hematoma</td>
<td>33%</td>
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<tr>
<td>evacuation of hematoma</td>
<td>13%</td>
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<tr>
<td>partial lobectomy</td>
<td>47%</td>
</tr>
<tr>
<td>debridement</td>
<td>13%</td>
</tr>
<tr>
<td>ventriculostomy</td>
<td>7%</td>
</tr>
<tr>
<td>intracranial pressure monitor</td>
<td>13%</td>
</tr>
<tr>
<td>none</td>
<td>7%</td>
</tr>
</tbody>
</table>

* GCS = Glasgow Coma Scale score; CT = computerized tomography.

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* RPMI 1640, fetal calf serum, HEPES buffer, L-glutamine, penicillin, and streptomycin supplied by GIBCO Laboratories, Grand Island, New York.

† Recombinant IL-2 provided by Cetus Corp., Emeryville, California.
sessed by trypan blue dye exclusion (always > 95%), and LAK cytotoxicity was determined.

**Incubation of PBMC Subpopulations**

In five head-injured patients and five normal subjects the ability of the lymphocyte-enriched and monocyte-enriched fractions to suppress cellular immune activity was evaluated. In all cases the cells were incubated with a lymphocyte-enriched cell population of $5 \times 10^6$ cells/ml in the presence of 500 U/ml of recombinant IL-2 for 72 hours at 37°C in 5% CO₂. Monocytes, when added, were incubated at a concentration of $5 \times 10^6$ cells/ml, thereby accounting for 10% of the PBMC population.

Toxicity of the LAK cells was determined under the following four experimental conditions: 1) following incubation of lymphocyte-enriched fractions from head-injured patients (controls consisted of lymphocytes from normal subjects); 2) following incubation of lymphocyte-enriched fractions from head-injured patients with PBMC’s from normal subjects (controls consisted of lymphocyte-enriched fractions from normal subjects incubated with PBMC’s from heterologous normal subjects); 3) following incubation of lymphocyte-enriched fractions from normal subjects with monocyte-enriched fractions from head-injured patients (controls consisted of lymphocyte-enriched fractions from normal subjects incubated with heterologous monocyte-enriched fractions from normal subjects); and 4) following incubation of lymphocyte-enriched fractions from head-injured patients incubated with monocyte-enriched fractions from normal subjects (controls consisted of lymphocyte-enriched fractions from head-injured patients incubated with heterologous monocyte-enriched fractions from head-injured patients).

**Evaluation of Serum From Head-Injured Patients**

The PBMC’s ($5 \times 10^6$ cells/ml) from five normal subjects were incubated with 5%, 10%, or 20% serum by volume from five head-injured patients with 500 U/ml of recombinant IL-2 for 72 hours at 37°C in 5% CO₂, and LAK cytotoxicity was determined. Controls consisted of PBMC’s ($5 \times 10^6$ cells/ml) from five normal subjects incubated with 5%, 10%, or 20% serum from five heterologous normal subjects.

**Determination of LAK Cytotoxicity**

The toxicity of LAK cells was determined by 4-hour $^{51}$Cr-release microcytotoxicity assays essentially as described by Klippel, et al. Effector cells were obtained as noted above and adjusted to a total cell concentration of $5 \times 10^6$ cells/ml. The target cells were Raji cells, a human Burkitt’s lymphoma cell line insensitive to natural killer cells maintained in long-term suspension and routinely processed twice each week in CM. The Raji cells were labeled with $^{51}$Cr by incubating $2 \times 10^6$ Raji cells with 150 μCi in 200 μl of CM for 2 hours at 37°C and 5% CO₂. The target cells were washed three times in CM and resuspended to a concentration of $5 \times 10^5$ cells/ml.

Next, 100 μl of effector cells ($5 \times 10^6$ cells/ml) was incubated with 100 μl of target cells ($5 \times 10^6$ cells/ml) for 4 hours at 37°C and 5% CO₂ for an effector:target ratio of 100:1. The maximum release (MR) of $^{51}$Cr was determined by incubation of target cells with 0.1 N HCl, and spontaneous release (SR) was determined by incubation of target cells with CM. Following incubation, the microtiter plates were centrifuged at 300 G for 5 minutes, and 100 μl of the supernatant was counted by a gamma counter. The percent of cytotoxicity was determined by the following formula: (ER − SR)/(MR − SR) × 100, where ER denotes experimental release. All assays were performed in triplicate.

**Results**

**Effect of Head Injury on LAK Cytotoxicity Generated by PBMC’s**

The effect of isolated severe head injury on LAK cytotoxicity generated by PBMC’s incubated alone or
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in the presence of PBMC's from normal subjects is summarized in Table 2. There was a significant decrease in LAK cytotoxicity when normal subjects were compared to head-injured patients (43% vs. 6%, p < 0.001). When PBMC's from head-injured patients were incubated with PBMC's from normal subjects, there was a significant suppression in cellular immune activity, resulting in a decrease of LAK cytotoxicity from 50% to 17% (p < 0.001).

**Effect of Lymphocytes From Head-Injured Patients on LAK Cytotoxicity**

We separated PBMC's into lymphocyte-enriched and monocyte-enriched populations in order to determine the contribution of each subpopulation of PBMC's from head-injured patients to the observed suppression of LAK cytotoxicity. As shown in Table 3, lymphocytes from head-injured patients have a decreased ability to generate LAK cytotoxicity: LAK cytotoxicity generated by lymphocytes from normal subjects was 42%, whereas that generated by lymphocytes from head-injured patients was 9% (p = 0.006). When PBMC's from normal subjects were incubated with lymphocytes from head-injured patients, LAK cytotoxicity was only 8%, compared to 33% for the control group (p < 0.001), indicating that lymphocytes from head-injured patients actively inhibit PBMC's from normal subjects.

**Effect of Monocytes From Head-Injured Patients on LAK Cytotoxicity**

As shown in Table 4, there was no significant difference in mean LAK cytotoxicity when comparing normal lymphocytes incubated with either monocytes from normal subjects (45%) to monocytes from head-injured patients (43%). In addition, there was no significant difference in mean LAK cytotoxicity when comparing head-injured patients' lymphocytes incubated with either monocytes from head-injured patients (9%) or normal subjects (12%).

**Effect of Serum From Head-Injured Patients on LAK Cytotoxicity**

Serum from head-injured patients was found to significantly inhibit LAK cytotoxicity generated by PBMC's of normal subjects in a dose-response manner (Table 5). Increasing the amount of serum used during the incubation from 5% to 10% or 20% by volume decreased mean LAK cytotoxicity by 10%, 28%, and 31%, respectively (obtained by subtraction of head-injured values from normal values). As shown in Table 5, serum from heterologous normal subjects, used as controls, had no significant effect on LAK cytotoxicity (p > 0.05).

**Discussion**

In a recent series of investigations, patients with severe head injury unaccompanied by other major systemic injuries were shown to have immune dysfunction. These changes included in vitro suppression of PHA-stimulated T-cell activation, suppression of IL-2 and INF-γ production without changes in interleukin-1 production, and suppression of LAK cytotoxicity. Additionally, in vitro PHA-stimulated cytokine production remained suppressed when incubation conditions were altered in order to account for the reduced percentage of helper T cells present in peripheral blood following head injury. These studies indicate that the function of effector lymphocytes, such as helper T cells and cytotoxic T cells, is suppressed following severe head injury.

The present study was undertaken in order to determine whether the suppression in effector lymphocyte function is associated with a subpopulation of suppressor PBMC's, such as suppressor lymphocytes or suppressor monocytes, or with immunosuppressive serum factors. Effector lymphocyte function was evaluated by determining in vitro LAK cytotoxicity. We selected LAK cytotoxicity because of its proven usefulness in documenting cellular immune function in a variety of clinical disorders associated with immune dysfunction. Additionally, LAK cytotoxicity is a useful screening test of effector lymphocyte function, having been shown to rely primarily on cytotoxic T-cell and helper T-cell function.

**Role of Suppressor Lymphocytes in Immune Suppression**

Although the individual roles of circulating lympho-

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**TABLE 4**

<table>
<thead>
<tr>
<th>Cell Populations</th>
<th>LAK Cytotoxicity (mean ± SE)</th>
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<tbody>
<tr>
<td>NL lymphocytes + 10% NL monocytes</td>
<td>45% ± 9%</td>
</tr>
<tr>
<td>NL lymphocytes + 10% HI monocytes</td>
<td>43% ± 5%</td>
</tr>
<tr>
<td>p value</td>
<td>0.4216</td>
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<tr>
<td>HI lymphocytes + 10% HI monocytes</td>
<td>9% ± 1%</td>
</tr>
<tr>
<td>HI lymphocytes + 10% NL monocytes</td>
<td>12% ± 2%</td>
</tr>
<tr>
<td>p value</td>
<td>0.1203</td>
</tr>
</tbody>
</table>

* Lymphocytes and monocytes obtained by plastic adhesion. LAK = lymphokine-activated killer; SE = standard error. Cell populations obtained from normal subjects (NL) and/or head-injured (HI) patients.
† Analysis of variance with multiple comparisons.

**TABLE 5**

<table>
<thead>
<tr>
<th>Incubation Conditions</th>
<th>LAK Cytotoxicity (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Serum</td>
<td>32% ± 4%</td>
</tr>
<tr>
<td>10% Serum</td>
<td>42% ± 3%</td>
</tr>
<tr>
<td>20% Serum</td>
<td>38% ± 5%</td>
</tr>
<tr>
<td>NL PBMC's + NL serum</td>
<td>22% ± 2%</td>
</tr>
<tr>
<td>HI serum</td>
<td>14% ± 2%</td>
</tr>
<tr>
<td>p value</td>
<td>0.067 &lt; 0.001 &lt; 0.001</td>
</tr>
</tbody>
</table>

* LAK = lymphokine-activated killer; SE = standard error; PBMC's = peripheral blood mononuclear cells. Cell populations obtained from normal subjects (NL) and/or head-injured (HI) patients.
† Analysis of variance with multiple comparisons.
cytes and monocytes in immune dysfunction have not been previously evaluated following severe head injury. Studies of immune function following central nervous system injury in animals have suggested that the splenic macrophages may play a significant role in immune suppression.\textsuperscript{31} Splenic macrophages have been shown to have an immunoregulatory function in animals with experimentally induced tumors and severe infections.\textsuperscript{1, 20, 21} It has been suggested that, following hypothalamic injury in animals, noncorticosteroid factors and direct neural innervation of primary and secondary lymphoid organs may affect splenic macrophages, which in turn act to regulate immune activity by lymphocytes.\textsuperscript{17, 31} In contrast, studies of immune function following severe systemic injury in humans has suggested possible roles for both suppressor lymphocytes and suppressor monocytes in the abrogation of cellular immune function.\textsuperscript{30, 13, 25, 34}

The results of our study suggest that the peripheral lymphocyte-enriched fraction of PBMC's from head-injured patients, and not the lymphocyte-enriched fraction, suppresses cellular immune activity following severe head injury. These suppressor lymphocytes depress in vitro LAK cytotoxicity generated by PBMC's from normal subjects, suggesting the presence of functional lymphocytes capable of actively suppressing effector lymphocyte function. Suppressor lymphocytes are classically believed to express the CD8+ phenotype; however, recent studies have shown that a second class of actively suppressing lymphocytes carries the CD4+/CD45R+ phenotype.\textsuperscript{32, 35} This latter lymphocyte, the suppressor/inducer T cell, normally represents only a small proportion of peripheral CD4+ lymphocytes. However, these cells have been shown to represent an unusually high proportion of the peripheral CD4+ lymphocyte population in a number of disease states associated with immune suppression.\textsuperscript{4, 24, 33, 35} In a recent series of experiments of PHA-stimulated PBMC's from head-injured patients, we observed that a disproportionately high percentage of T cells were of the CD4+/CD45R+ (suppressor/inducer) phenotype relative to the percent of T cells expressing the CD4+/CDw29+ (helper/inducer) phenotype.\textsuperscript{30} Although this observation is consistent with our finding that the subpopulation of PBMC's responsible for immunosuppression is of the lymphocyte subclass, the phenotype of lymphocytes responsible for suppressing effector lymphocyte function following severe head injury has not been determined.

Role of Serum Factors in Immune Suppression

In view of the rapidity with which cellular immune activity is suppressed following isolated severe head injury in man, it has been suggested that serum factors may be responsible for the induction of immuno-suppression.\textsuperscript{32} Soluble factors, generally low-molecular-weight peptides that have not been fully characterized, have been isolated in a variety of clinical disorders that result in immune dysfunction.\textsuperscript{13, 6, 18, 40} In addition, investigations of immune function in animals and man have demonstrated that a variety of factors can affect immune activity; these include neurotransmitters such as serotonin, various hormonal factors, and neuropepti- des such as methionine-enkephalin.\textsuperscript{11, 12, 15, 30, 38} The results of this study indicate that serum factors are present following isolated severe head injury and that these factors suppress LAK cytotoxicity in a dose-dependent manner. This finding may be of importance in understanding the mechanisms by which immune function is altered following severe head injury. These factors may directly suppress lymphocyte function by enhancing suppressor lymphocyte activity. Further investigations designed to characterize these factors and their specific mechanism of action are indicated.

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