EFFECTS OF HEAD TRAUMA AND BRAIN INJURY ON
NEUROENDOCRINOLOGIC FUNCTION

ANNUAL REPORT

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Robert W. Hamill, M.D.
Joseph V. McDonald, M.D.

September 6, 1985

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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University of Rochester Medical Center
Rochester, New York 14642

DOD DISTRIBUTION STATEMENT
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The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.
Patients with traumatic injury, admitted within 48 hours of their accident were studied to determine the association between the severity of injury assessed by standard techniques and sympathetic nervous system function in order to determine whether 1) catecholamine levels can be used to predict patient outcome, and 2) whether excessive catecholamine release contributes to morbidity and mortality. During the period covered by this report, 50 patients (88 over the two years of the contract) with head injury were studied, of whom 14 had systemic trauma and 3 had spinal cord injuries. In the later phases of the reporting period, patients with systemic, but not brain injuries, were enrolled and 8 such patients were enrolled.
Investigation of the catecholamine response to traumatic brain injury revealed that admission catecholamine levels in patients with severe neurologic impairment (GCS 3/4), who were otherwise indistinguishable, separates patients into those likely to have significant neurologic improvement at one week from those who will die or remain severely impaired. Catecholamines over the initial week of hospitalization also correlated with the severity of injury as assessed by the Glasgow Coma Score and with the Injury Severity Score in multi-traumatized patients. Furthermore, admission catecholamine concentrations correlated with the extent of head injury as assessed by CT scans, with the length of time the patient remained on a respirator, the length of hospital stay, the Glasgow Outcome Scale as well as with the severity of the gonadal insufficiency. Thus, measurement of sympathetic nervous system activation can be used for an internally derived marker of patient morbidity and mortality and hence appears to be an important marker for determining patient outcome.-The exceedingly high catecholamine levels in patients with severe neurologic impairment who fail to improve suggest that the catecholamines themselves may be contributing to the poor prognosis.
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Summary

The purpose of this project was to determine whether the magnitude of sympathetic nervous system activation reflects the severity of traumatic brain injury and thus, whether assessment of circulating catecholamine levels would be useful in predicting patient morbidity and mortality. Conversely, examination of the question of whether hyperstimulation of the adrenergic component of the sympathetic nervous system is maladaptive needed to be addressed. Part of these investigations were also designed to study the interactions of traumatic brain injury with neuroendocrine function, particularly gonadal. Patients 18 years of age or over, admitted to Strong Memorial Hospital with 48 hours of receiving traumatic brain injury of any severity, were studied. Blood for catecholamines and pituitary hormones were obtained on admission and twice daily thereafter. The values obtained were correlated with the neurological examination and with CT scan findings.

Our results indicate that admission catecholamine levels in patients with severe neurologic impairment (GCS 3/4) who were otherwise indistinguishable, separated patients into those likely to have significant neurologic improvement at one a week, from those who would die or remain severely impaired. Catecholamines also correlated with Glasgow Coma Score levels over the initial week of hospitalization, while admission catecholamine concentrations correlated with the extent of head injury as assessed by CT scans, with the Injury severity Scale, with the length of time the patient remains on a respirator, the length of hospital stay, the Glasgow Outcome Scale as well as with the severity of the gonadal insufficiency. Thus, measurement of sympathetic nervous system activation can be used for an internally derived marker of patient morbidity and mortality and hence appears to be an important marker for determining patient outcome.

Foreword.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.
BODY

The second yearly report covers a period from May 15, 1984 through June 30, 1985. The time span of this report has been lengthened modestly in order for the Quarterly Reports and Yearly Reports to coincide. During this period, 50 patients with head injury were studied. In 14 of these, systemic trauma was also present while spinal cord injury was present in three other patients. Fifteen patients with other acute neurologic problems were studied during this interval including; seven with intracerebral hemorrhage, two with subarachnoid hemorrhage, two with anoxic brain injury and one with a penetrating wound of the brain. Thirty-two patients who were acutely ill served as non-neurological control groups. Polytrauma without brain injury was present in about eight of these, while 24 had a variety of acute medical and surgical problems.

Thus, for the two years of the contract, we have studied 88 patients with traumatic head injury, 39 patients with acute non-traumatic neurologic disease predominantly vascular CNS disorders, and 50 patients with acute non-neurologic disorders including multiple systemic trauma.

The following hormonal determinations were performed during the past year: catecholamines, both free and conjugated, 624; cortisol, 1171; ACTH, 44; beta-endorphin, 78; LH, 283; FSH, 284; testosterone, 40; growth hormone, 239; prolactin, 40; TSH, 187; T	extsubscript{4}, 236; T	extsubscript{3}, 133; free T	extsubscript{4}, 178; DHEAS, 220; androstenedione, 144; 17-hydroxyprogesterone, 144.

B. Specific Projects

As our patient base increased in size, attention was turned increasingly to our first Specific aim; namely, investigation of the sympathetic nervous system response to traumatic brain injury while our investigation of the pituitary and gonadal responses to head trauma and acute illness were brought to a successful conclusion.

1. Catecholamines as a marker of injury severity.

As described in more detail below, analysis of our catecholamine data reveals strong associations between catecholamine levels and a variety of clinical parameters (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of Pilot Studies Demonstrating Significant Correlations Between SNS Activation and Patient Morbidity and Mortality</strong></td>
</tr>
<tr>
<td>1. Neurologic improvement at one week vs. death or continued severe impairment in GCS 3/4 patients.</td>
</tr>
<tr>
<td>2. Glasgow Coma Score levels over initial week of hospitalization.</td>
</tr>
<tr>
<td>3. Pulse rate and blood pressure.</td>
</tr>
<tr>
<td>4. Injury Severity Scale (ISS).</td>
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<td>5. Head Injury Severity Scale (HISS).</td>
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<tr>
<td>7. Length of hospital stay.</td>
</tr>
<tr>
<td>8. Glasgow Outcome Scale</td>
</tr>
</tbody>
</table>

We have expanded our initial observations presented in the first Annual Report that there is strong correlation between the Glasgow Coma Score and norepinephrine, epinephrine and dopamine concentrations. To date, 21 patients who were GCS 3/4 on entry had catecholamine levels obtained within 48 hours of injury. Using norepinephrine concentrations of 1300 pg/mL as a cutoff, only 11% of patients with values above this level had a good outcome at one week (GCS > 11), while 67% of patients with norepinephrine
concentrations less than 1300 pg/mL had such an improvement. Furthermore, all patients with norepinephrine levels below 900 pg/mL improved. Comparison of norepinephrine levels between the groups who died or remained GCS 3/4 versus those who improved to GCS > 11 revealed a highly significant difference (p < 0.02) (Figure 1). Indeed, when the data were analyzed by catecholamine levels, irrespective of GCS from the entire cohort of 51 patients, 17 of 19 patients with high norepinephrine concentrations, either died or had profound neurologic impairment requiring institutionalization. Thus, using a

modification of the Glasgow Outcome Score in which patients were evaluated at the time of discharge or transfer from Strong Memorial Hospital, it is apparent that admission catecholamine levels segregate patients by prognosis (Table 2).

Table 2

<table>
<thead>
<tr>
<th>GOS</th>
<th>GR</th>
<th>MD</th>
<th>SD</th>
<th>PV</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5</td>
<td>16</td>
<td>15</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>NE*</td>
<td>484</td>
<td>530</td>
<td>826</td>
<td>1360</td>
<td>1992</td>
</tr>
<tr>
<td>E*</td>
<td>162</td>
<td>101</td>
<td>195</td>
<td>396</td>
<td>486</td>
</tr>
<tr>
<td>DA*</td>
<td>68</td>
<td>58</td>
<td>65</td>
<td>73</td>
<td>814</td>
</tr>
</tbody>
</table>

GR = good recovery; MD = moderate disability; SD = severe disability; PV = persistant vegetation; D = death.
N = patient number
* pg/mL
Patients who died, or remained persistently vegetative, had admission of norepinephrine or epinephrine levels significantly greater than those with better outcomes. These data are also reflected in the correlation between norepinephrine and dopamine levels and the length of time on a respirator in patients surviving beyond one week ($r = 0.52, p < 0.05$ and $r = 0.54, p < 0.05$). This is further reflected in the significant association between plasma norepinephrine levels and length of hospitalization (Figure 2).

In collaboration with our neuroradiologist, Dr. Dan Kido, we have developed a new anatomic index of head injury based upon the anatomic scoring of injury severity according to the AIS-80 (Committee on Injury Scaling: The abbreviated Injury Scale: 1980 Revision. American Association for Automotive Medicine, Morton Grove, II, 1980), utilizing modifications of the injury severity scale devised by Baker et al. (J. Trauma 23:183, 1983). Each of the three worst head injuries and the duration of coma was coded and the relative weights squared and then summed. Correlation of the logarithm of each catecholamine and the logarithm of the Head Injury Severity Scale (HISS) are highly significant in each case. The
data for norepinephrine is shown in Figure 3. Clinical utility of this new index is

![Graph showing correlation between HISS and norepinephrine levels.](image)

...demonstrated by the highly significant correlations in these 63 patients between the HISS and both the admission Glasgow Coma Score ($r = 0.73, p < 0.0001$) and the Glasgow Outcome Score ($r = 0.70, p < 0.0001$).

In the latter half of the past year, we began to evaluate the effects of systemic injury with or without head injury on sympathetic nervous system activation. To date, 16 patients have been studied. While the numbers are small, the data demonstrate a high degree of correlation between the Injury Severity Scale (ISS) and norepinephrine ($r = 0.52, p < 0.04$) and epinephrine ($r = 0.63, p < 0.01$) levels. These exciting preliminary observations suggest that our central hypothesis, i.e. the determination of sympathetic nervous system activation in traumatic injury, will provide important and useful information in determining the severity of the stress and predict outcome, will be useful in broader classes of patients than those with only head injury.

2. Studies of pituitary gonadal function.

...During the second year of this project, investigation of our observations that hypogonadism develops following acute severe illness was brought to a close. Our initial studies investigating the specificity of the etiology of the hypogonadism and the site (hypothalamic, pituitary or gonadal) were described in great detail in the previous Annual Report and were published in *The Journal of Endocrinology and Metabolism, 64:444, 1985*. Additional studies were completed investigating the
possible role of the sympathetic nervous system in these alterations and whether the sex steroid precursors were also affected.

Patients were divided into two groups based upon the severity of neurologic dysfunction — Group 1, Glasgow Coma Score (GCS) < 8, Group 2 ≥ 8. Group 1 was further divided into those patients treated with dexamethasone (Group 1b) and those who weren’t (Group 1a). Testosterone, dihydrotestosterone, androstenedione, 17-hydroxyprogesterone, DHEA sulfate, cortisol, LH, FSH, and the catecholamines norepinephrine, epinephrine and dopamine were measured in 31 acutely brain injured men, ages 18-95, shortly after their accident and again four days after it. Testosterone fell 53% (p < 0.001) in 13 Group 1a men, but only 25% (p = NS) in the less severely injured and their testosterone, 17-hydroxyprogesterone, and DHEA sulfate levels were significantly lower than normal on day four. LH and FSH levels were also significantly reduced. In the eight men treated with dexamethasone (8-40 mg/day) (Group 1b), the decrease in testosterone, LH and FSH concentrations were similar to those present in Group 1a. In all patients, admission NE and EPI were elevated (NE: 841 ± 105 pg/ml; EPI: 191 ± 32 pg/ml and there were highly significant inverse correlations between admission norepinephrine (r = -0.52, p < 0.005) (Fig. 4) and epinephrine levels and day four testosterone concentrations. Thus, severe traumatic brain injury leads to hypogonadotropic hypogonadism which affects testosterone and its precursors. The magnitude of the gonadal dysfunction is dependent upon the severity of the neurologic insult. Finally, the decrease in testosterone is significantly correlated with admission catecholamine levels, suggesting a role for the SNS in mediating this response in men.

Therefore, not only does activation of the sympathetic nervous system correlate with the severity of the neurologic insult, but it appears to be also involved in mediating one aspect of endocrinologic dysfunction, namely hypogonadism.
Papers, Abstracts or Presentations Resulting From the Second Year of Support by This Contract.

Papers


Presentations:


Glossary.

DA  Dopamine
E   Epinephrine
GCS Glasgow Coma Score
HISS Head Injury Severity Scale
ISS  Injury Severity Scale
NE  Norepinephrine