Hypothalamic hypothyroidism and hypogonadism in prolonged traumatic coma

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Prolonged coma after head trauma is associated with depletion of 3',5'-cyclic adenosine monophosphate (cAMP) in the cerebrospinal fluid (CSF). Because cAMP has previously been implicated in neuroendocrine secretion, this study examines the pituitary-hypothalamic function in 15 adult male patients (to exclude the effects of puberty and menses) with traumatic coma lasting longer than 2 weeks. Ventricular CSF cAMP was measured at 2- to 4-day intervals for 10 to 25 days. Simultaneously, plasma hormone concentrations were also determined.

In all 15 cases, CSF cAMP and plasma levels of thyroid-stimulating hormone (TSH), thyroxine (T₄), free T₄, triiodothyronine (T₃), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone became subnormal. In 11 patients whose level of consciousness fluctuated, the reduction in plasma T₄ and testosterone were proportional to both severity of coma (r > 0.81, p < 0.05) and depletion of CSF cAMP (r > 0.81, p < 0.05). In four patients who remained deeply comatose for 17 to 25 days, the hypothyroidism and hypogonadism persisted. In six patients who regained consciousness, both endocrine defects improved partially or completely. Injection of 1) thyrotrophic-releasing hormone and 2) gonadotrophic-releasing hormone elicited normal or supernormal increases in plasma concentrations of 1) TSH, and 2) LH and FSH, reduced, respectively, suggesting a suprahypophyseal deficiency. These observations demonstrate that suprahypophyseal hypothyroidism and hypogonadism may occur regularly in patients with traumatic coma lasting longer than 2 weeks.

KEY WORDS □ traumatic coma □ cAMP □ hypogonadism □ suprahypophyseal hypothyroidism

RECENT studies have demonstrated that prolonged coma after severe craniocerebral trauma is associated with a reduction in 3',5'-cyclic adenosine monophosphate (cAMP) in the ventricular cerebrospinal fluid (CSF) to markedly subnormal values which correlate significantly with prognosis.¹⁰,²⁸ It is known that cAMP is involved in neuroendocrine secretion. Produced within adenohypophyseal cells, cAMP is believed to mediate release of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in response to the corresponding hypothalamic releasing factors, thyrotrophic-releasing hor-
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TABLE 1
Clinical data of the 15 male patients with coma following head trauma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Traumatic Lesions*</th>
<th>Neurosurgical Procedure†</th>
<th>coma</th>
<th>Coma Grade on Admission</th>
<th>Period of Dexamethasone Treatment (days)‡</th>
<th>Period of Data Collection (days)§</th>
<th>Number of Test Days$</th>
<th>Coma Grade at End of Data Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>It acute SDH</td>
<td>evacuation of hematoma</td>
<td>III</td>
<td>1-18</td>
<td>6-31</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>intracerebral</td>
<td>evacuation of hematoma</td>
<td>III</td>
<td>1-25</td>
<td>7-25</td>
<td>7</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>cerebral contusion</td>
<td>none</td>
<td>III</td>
<td>1-5</td>
<td>7-17</td>
<td>5</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>cerebral contusion</td>
<td>none</td>
<td>III</td>
<td>1-8</td>
<td>7-25</td>
<td>7</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>bilateral sub-acute SDH</td>
<td>removal of hematoma</td>
<td>III</td>
<td>1-18</td>
<td>7-18</td>
<td>5</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>intracerebral</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-13</td>
<td>7-33</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>none</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-8</td>
<td>6-19</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>acute SDH</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-10</td>
<td>6-20</td>
<td>7</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>cerebral</td>
<td>temporal lobectomy</td>
<td>III</td>
<td>1-7</td>
<td>7-22</td>
<td>6</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>acute epidural</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-9</td>
<td>7-19</td>
<td>8</td>
<td>IV</td>
<td>IV</td>
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<tr>
<td>11</td>
<td>48</td>
<td>subacute SDH</td>
<td>evacuation of hematoma</td>
<td>III</td>
<td>1-11</td>
<td>7-18</td>
<td>9</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>12</td>
<td>27</td>
<td>intracerebral</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-7</td>
<td>6-29</td>
<td>9</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>acute SDH</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-3</td>
<td>6-27</td>
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<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>14</td>
<td>26</td>
<td>acute epidural</td>
<td>evacuation of hematoma</td>
<td>IV</td>
<td>1-7</td>
<td>7-23</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>39</td>
<td>cerebral</td>
<td>temporal lobectomy</td>
<td>III</td>
<td>1-14</td>
<td>7-20</td>
<td>8</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

*As revealed by computerized tomography. SDH = subdural hematoma.
†Procedures other than insertion of ventricular catheter connected to subcutaneous Rickham reservoir.
‡Day 1 = day of head trauma.
§Days on which values shown in Table 2 were measured.

mone (TRH) and gonadotrophic-releasing hormone (GnRH).4,18,21,30,32-34 In addition, there is some evidence that suggests that the secretion of the releasing factors themselves into the hypothalamic portal capillaries may be influenced by cAMP formed within hypothalamic neurons under the influence of bioactive amines.2,3,7,19,20

The objective of the present study was to investigate the influence of prolonged traumatic coma on neuroendocrine secretion. Any changes observed that correlated with the reduction in CSF cAMP would suggest that a disorder of brain metabolism of cAMP may be responsible for alteration of secretion of pituitary hormones.

Clinical Material and Methods

Fifteen adult men, 24 to 53 years of age, were hospitalized in Grade III or IV coma at Grady Memorial Hospital, Atlanta, Georgia, within 4 hours of sustaining head trauma (Table 1). We selected adult males for study to exclude the effects of puberty and the menstrual cycle. Each patient remained comatose for at least 2 weeks. The level of coma was classified as follows:

Grade 0: normal.
Grade I: drowsy, lethargic, indifferent and uninterested, or belligerent and uncooperative; does not
**TABLE 2**

*Plasma hormones and CSF cAMP in normal subjects and in patients during Days 6 to 33 after head trauma*

<table>
<thead>
<tr>
<th>Group</th>
<th>Grade of Coma</th>
<th>TSH (μU/ml)*</th>
<th>T4 (μg/100 ml)</th>
<th>Free T4 (ng/100 ml)</th>
<th>T3 (ng/100 ml)</th>
<th>LH (ng/ml)</th>
</tr>
</thead>
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<tr>
<td>normals</td>
<td>0 (n = 8)†</td>
<td>3.14 ± 0.4</td>
<td>7.93 ± 0.6</td>
<td>1.75 ± 0.1</td>
<td>116.9 ± 9</td>
<td>3.20 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>0 (n = 7)</td>
<td>2.71 ± 0.1</td>
<td>7.92 ± 0.39</td>
<td>1.81 ± 0.13</td>
<td>91.5 ± 8.2</td>
<td>2.34 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>I (n = 9)</td>
<td>1.53 ± 0.11‡</td>
<td>6.21 ± 0.83</td>
<td>1.32 ± 0.24</td>
<td>80.8 ± 5.4‡</td>
<td>1.88 ± 0.49</td>
</tr>
<tr>
<td></td>
<td>II (n = 8)</td>
<td>.81 ± 0.16‡</td>
<td>4.21 ± 0.61‡</td>
<td>.81 ± 0.09‡</td>
<td>63.2 ± 8.9‡</td>
<td>1.21 ± 0.22‡</td>
</tr>
<tr>
<td></td>
<td>III (n = 15)</td>
<td>.88 ± 0.16‡</td>
<td>3.11 ± 0.24‡</td>
<td>.61 ± 0.02‡</td>
<td>38.6 ± 2.9‡</td>
<td>.62 ± 0.06‡</td>
</tr>
<tr>
<td></td>
<td>IV (n = 10)</td>
<td>.54 ± 0.04‡</td>
<td>2.21 ± 0.23‡</td>
<td>.66 ± 0.05‡</td>
<td>31.7 ± 3.9‡</td>
<td>.38 ± 0.05‡</td>
</tr>
<tr>
<td></td>
<td>V (n = 3)</td>
<td>&lt;1.0</td>
<td>1.80</td>
<td>.40</td>
<td>34.0</td>
<td>.55</td>
</tr>
</tbody>
</table>

*Values of plasma TSH below the limit of detection (<1 μU/ml) were considered zero in calculating average ± SE.
†Three of the normal controls were at some time in the study in the specified stage of coma.
‡p < 0.05 for difference between this value and corresponding value of normal group.

Lapse into sleep when left undisturbed.

Grade II: stuporous, will lapse into sleep when not disturbed; may be disoriented to time, place, and person.

Grade III: deep stupor, requires strong pain to evoke movement, may have focal neurological signs but will respond appropriately to noxious stimuli.

Grade IV: does not respond appropriately to any stimuli; may exhibit decerebrate or decorticate posturing; retains deep tendon reflexes; may have dilated pupils, absent corneal or oculocarotid reflexes.

Grade V: does not respond appropriately to any stimuli; flaccid, no deep tendon reflexes; usually apneic.

A ventricular catheter connected to a subcutaneous implanted reservoir was placed in the frontal horn of a lateral ventricle within a few hours after admission to monitor intracranial pressure and aid in the treatment of intracranial hypertension. All patients were treated from the time of admission with 6 mg dexamethasone, four times daily, which was continued for 3 to 25 days (Table 1). Other aspects of diagnosis and treatment are given in Table 1.

To evaluate the neuroendocrine function in these patients, the following plasma concentrations were measured at 8 a.m. every 2 to 4 days in each patient, beginning on Day 6 or 7, and ending on day 17 to 33: LH, FSH, TSH, growth hormone (GH), prolactin, testosterone, thyroxine (T4), free T4, triiodothyronine (T3). Simultaneously, ventricular CSF samples were removed for cAMP analysis. In five patients, during a period when T4 and T3 were known to be subnormal, TRH was administered to evaluate the ability of the pituitary gland to release TSH. In each of these patients when plasma testosterone was known to be subnormal, a GnRH test was run to evaluate pituitary release of FSH and LH. In all 15 patients, dexamethasone was discontinued when clinically indicated. Beginning 7 days thereafter, plasma cortisol was measured at 8 a.m. and 4 p.m. at 2- to 4-day intervals. To monitor endogenous antidiuretic hormone function, fluid intake and output were measured daily, and serum and urine osmolality twice a week.

The hormonal analyses of plasma, and the TRH and GnRH provocative tests, were also
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**TABLE 2 (Continued)**

<table>
<thead>
<tr>
<th>Plasma Hormones</th>
<th>Testosterone (ng/100 ml)</th>
<th>Cortisol (µg/100 ml)</th>
<th>HGH (ng/ml)</th>
<th>Prolactin (ng/ml)</th>
<th>CSF cAMP (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8 a.m.</td>
<td>4 p.m.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3.73 ± 0.4</td>
<td>818.8 ± 66</td>
<td>15.0 ± 1.0</td>
<td>9.1 ± 1.0</td>
<td>2.43 ± 0.4</td>
<td>18.5 ± 2</td>
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<tr>
<td>2.39 ± 0.84</td>
<td>274.0 ± 93</td>
<td>22.8 ± 2.4</td>
<td>16.8 ± 1.3</td>
<td>1.85 ± 0.3</td>
<td>18.4 ± 6</td>
</tr>
<tr>
<td>2.20 ± 0.33</td>
<td>212.4 ± 62</td>
<td>16.2 ± 1.9</td>
<td>13.4 ± 1.7</td>
<td>1.52 ± 0.33</td>
<td>16.5 ± 5.4</td>
</tr>
<tr>
<td>1.85 ± 0.49‡</td>
<td>82.1 ± 16‡</td>
<td>15.6 ± 2.3</td>
<td>12.9 ± 2.5</td>
<td>1.49 ± 0.23</td>
<td>18.2 ± 5.3</td>
</tr>
<tr>
<td>.84 ± 0.04‡</td>
<td>35.6 ± 3.8‡</td>
<td>—</td>
<td>—</td>
<td>2.37 ± 0.33</td>
<td>18.0 ± 1.3</td>
</tr>
<tr>
<td>.66 ± 0.06‡</td>
<td>24.4 ± 4.2‡</td>
<td>—</td>
<td>—</td>
<td>1.88 ± 0.29</td>
<td>18.5 ± 0.74</td>
</tr>
<tr>
<td>.54</td>
<td>&lt; 20</td>
<td>—</td>
<td>—</td>
<td>1.36</td>
<td>17.4</td>
</tr>
</tbody>
</table>

‡p <0.05 for difference between this value and corresponding value of normal group.

performed in eight healthy subjects aged 24 to 39 years.

**Results**

In each of the 15 patients, the battery of plasma hormone and CSF cAMP analyses shown in Table 2 was measured from 5 to 11 times. A total of 78 sets of data was obtained. Mean and standard error (SE) were recorded for each patient who had more than one battery of measurements for a particular coma grade. For example, in Table 2, for Grade II coma “n = 8” means that eight of the 15 patients exhibited Grade II coma at some time in the study; therefore, each patient at a particular coma grade is represented one time at most. Table 2 shows that plasma GH, prolactin, and cortisol concentrations in the comatose patients generally did not differ from normal. However, plasma testosterone, LH, FSH, T₄, T₃, TSH, and ventricular CSF cAMP were all subnormal. These reductions were directly proportional to the severity of coma (p < 0.05). Testosterone was more severely depleted during coma than T₄. In Grade IV coma, testosterone was less than 5% of the normal mean while T₄ averaged 30% of normal in the same cases. The CSF cAMP was inversely related to coma level, and directly related to plasma T₄ and plasma testosterone. Correlations between these four variables were significant at p < 0.05. The time relationships among coma, CSF cAMP, testosterone, and T₄ in four representative patients are illustrated in Fig. 1. Initial observations, made on Day 6 or 7, when the patient was in Grade III or IV coma, usually showed that testosterone was less than 50 ng/100 ml (normal 300 to 1200 ng/100 ml), T₄ was 2 to 4 µg/100 ml (normal 4.5 to 11.5 µg/100 ml), and CSF cAMP was less than 9 nM (normal 15 to 25 nM). Testosterone was usually at its lowest level by Day 6 or 7, while T₄ declined maximally (about 2 µg/100 ml) around Day 10 to 15. When deep coma persisted, plasma T₄, testosterone and CSF cAMP continued to be subnormal. However, when coma improved, a parallel return toward normal was observed in CSF cAMP, and in plasma testosterone and T₄. Seven patients regained normal consciousness (Grade 0) during the period of observation. In all seven individuals, plasma T₄, and T₃ simultaneously returned to the normal range. Plasma testosterone also rose in all seven, but in two of the patients it did not regain the normal range during the period of observation.

When TRH and GnRH were injected on separate days in cases 1 to 5 during periods of
Grade II to IV coma, subnormal plasma T4 and testosterone were demonstrated. The same tests were done with eight normal controls. The results showed that FSH, LH, and TSH increased with the administration of the appropriate releasing factor (Fig. 2). There was no significant difference (p > 0.05) between comatose and normal subjects in the rise of plasma LH and FSH after injection of GnRH (FSH data are not shown in Fig. 2). However, the increase in plasma TSH after TRH was significantly greater in the comatose than in the normal group (p < 0.05).

Urine volume remained below 3000 ml/day in all 15 patients, and serum osmolality was generally in the normal range of 280 to 300 mOsm.

Discussion

The present study confirms in an additional 15 cases the earlier observation of diminished ventricular CSF cAMP concentration inversely proportional to the severity of coma following severe craniocerebral trauma. This prolonged coma and reduction of ventricular CSF cAMP were, in addition, associated with abnormally low plasma concentrations of testosterone, T4, free T4, and T3. Hypothyroidism and hypogonadism were evident by the seventh day after coma-producing craniocerebral trauma. With rising CSF cAMP and improvement in the level of consciousness, the two endocrine defects resolved partially (testosterone) or completely (T4). Both the hypothyroidism and hypogonadism were of suprahypophyseal origin.

Fig. 1. Clinical course of four representative patients. Lower limits of normal ranges for CSF cAMP (nM), plasma T4 (µg/100 ml), and plasma testosterone (ng/100 ml) are indicated by the broken lines.

Fig. 2. Results of provocative tests with thyrotrophic-releasing hormone (TRH) (above) and gonadotrophic-releasing hormone (GnRH) (below) on five comatose and eight normal subjects. Horizontal axis: minutes before or after intravenous injection of the releasing factor (500 µg of TRH or 100 µg of GnRH). Vertical axis: plasma concentration of luteinizing hormone (LH) or thyroid-stimulating hormone (TSH). Each point shows average ± SE. N = normal; C = comatose.
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origin, as evidenced by the subnormal values of plasma LH, FSH, and TSH, by the normal responses of plasma LH and FSH to injection of GnRH, and by the supernormal response of plasma TSH to TRH.

No abnormality was detected in the other adenohypophyseal functions studied; however, one or more additional defects in hypothalamic-pituitary function are not definitely excluded. The normal plasma prolactin level during coma suggests the preservation of the hypothalamic release of prolactin-release-inhibitory factor. Since provocative tests of GH release were not used, a defect in GH secretion has not been ruled out. Tests of pituitary adrenocorticotropic hormone reserve and of melanocyte-stimulating hormone secretion were not done. From the normal or elevated plasma levels of cortisol in the comatose subjects after dexamethasone was stopped (Table 2), we infer that endogenous corticotropic-releasing factor, unlike TRH and GnRH, continued to be secreted during coma. Whether adrenocorticotropic hormone (ACTH) secretion was entirely unaffected in the comatose patients, however, is uncertain. Table 2 shows that the cortisol levels in Grade 0 patients (after recovery from coma) were 50% to 80% higher than those of normal subjects. During Grade I and II coma, the cortisol levels returned to normal. This discrepancy is not understood at present.

The possible role of dexamethasone in causing the hypothyroidism should be considered. Administration of 24 mg of this steroid daily for 2½ to 5 days to normal subjects causes a decline in serum TSH, T3, and free T4 concentrations; T4 and free T3 are unaffected.4,24,26 Because the TSH response to TRH is simultaneously blunted, the steroid is believed to suppress pituitary TSH secretion. Accordingly, dexamethasone probably contributed to the hypothyroidism of our comatose patients, but it was not the major cause, for the following reasons: 1) during the period of hypothyroidism, release of endogenous TSH in response to exogenous TRH was not impaired; 2) T4 and free T3 were subnormal; and 3) in patients who remained deeply comatose for 12 to 27 days after dexamethasone was stopped, the hypothyroidism persisted with little or no improvement.

Our data indicate that the adenohypophysis of the comatose patient was not releasing TSH and gonadotropins in adequate amounts primarily because it was not being stimulated by endogenous TRH and GnRH. The mechanism responsible for this deficit in releasing factors remains uncertain, although it is well known that severe head trauma is frequently associated with significant pathological changes within the hypothalamus. The hypothyroidism and hypogonadism followed the same general time course as the reduction in CSF cAMP, although hormone recovery occasionally preceded return of CSF cAMP level to normal (Fig. 1). This temporal association, however, may be of no significance, since two concurrently observed abnormalities imply no cause and effect. It also seems unlikely that a disorder of cAMP metabolism within the brain would selectively affect only three of the six pituitary hormones studied. Perhaps the deficit in TRH and GnRH, and the decline in CSF cAMP both resulted independently from a disturbance in the function of bioactive monoamines within the brain which are known to influence the secretion of hypothalamic releasing factors, the activity of brain adenylate cyclase, which is necessary for the synthesis of cAMP, and the concentration of CSF cAMP. Another possible mechanism for the failure of TRH and GnRH to reach the pituitary gland after head trauma is interruption of the portal circulation flowing from the hypothalamus to the pituitary gland. The intravenously injected exogenous releasing factors could still reach the anterior lobe via the hypophyseal arteries. This seems unlikely since other releasing factors as well as prolactin-inhibiting factor should be affected as well. Finally, head trauma could activate hypothalamic peptidases capable of destroying TRH and GnRH.

Hypogonadism is of little clinical significance in the comatose patient. However, hypothyroidism is potentially important since deficiency of thyroid hormones can cause additional brain dysfunction as well as systemic effects. Indeed, myxedema can cause coma independently. Our preliminary experience, however, in treating with hormone replacement a small number of hypothryoid patients, who were stuporous or comatose for a prolonged period of time following head trauma, has not resulted in any dramatic improvement in level of consciousness. It is likely that the hypothyroidism observed represents only one of several possible factors

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that may contribute to traumatic coma. It is therefore suggested that patients with prolonged stupor after head trauma should be monitored for this correctible acute endocrine problem.

References

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