

Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report

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Object. Recognition of pituitary hormonal insufficiencies after head injury and aneurysmal subarachnoid hemorrhage (SAH) may be important, especially given that hypopituitarism-related neurobehavioral problems are typically alleviated by hormone replacement. In this prospective study the authors sought to determine the rate and risk factors of pituitary dysfunction after head injury and SAH in patients at least 3 months after insult.

Methods. Patients underwent dynamic anterior and posterior pituitary function testing. Results of the tests were compared with those of 18 age-, sex-, and body mass index–matched healthy volunteers. The 22 head-injured patients included 18 men and four women (mean age 28 ± 10 years at the time of injury) with initial Glasgow Coma Scale (GCS) scores of 3 to 15. Eight patients (36.4%) had a subnormal response in at least one hormonal axis. Four were growth hormone (GH) deficient. Five patients (four men, all with normal testosterone levels, and one woman with a low estradiol level) exhibited an inadequate gonadotroph response. One patient had both GH and thyrotroph deficiency and another had both GH deficiency and borderline cortisol deficiency. At the time of injury, all eight patients with pituitary dysfunction had an initial GCS score of 10 or less and, compared with the 14 patients without dysfunction, were more likely to have had diffuse swelling, seen on initial computerized tomography scans ($p < 0.05$), and to have sustained a hypotensive or hypoxic insult ($p = 0.07$). Of two patients with SAH who were studied (Hunt and Hess Grade IV) both had GH deficiency.

Conclusions. From this preliminary study, some degree of hypopituitarism appears to occur in approximately 40% of patients with moderate or severe head injury, with GH and gonadotroph deficiencies being most common. A high degree of injury severity and secondary cerebral insults are likely risk factors for hypopituitarism. Pituitary dysfunction also occurs in patients with poor-grade aneurysms. Postacute pituitary function testing may be warranted in most patients with moderate or severe head injury, particularly those with diffuse brain swelling and those sustaining hypotensive or hypoxic insults. The neurobehavioral effects of GH replacement in patients suffering from head injury or SAH warrant further study.

KEY WORDS • traumatic brain injury • aneurysmal subarachnoid hemorrhage • hypopituitarism • growth hormone deficiency • cerebral swelling

PITUITARY function assessment is an infrequent consideration in the acute or long-term management of patients sustaining traumatic brain injury or aneurysmal SAH. However, both head injury and SAH pose significant risk to pituitary function, given the gland's bony encasement within the sella turcica, its delicate infundibular hypothalamic structures, and its vulnerable

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; BMI = body mass index; CPP = cerebral perfusion pressure; CT = computerized tomography; DI = diabetes insipidus; FSH = follicle-stimulating hormone; GCRC = General Clinical Research Center; GCS = Glasgow Coma Scale; GH = growth hormone; GnRH = gonadotropin-releasing hormone; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; IGF-I = insulin-like growth factor I; ITT = insulin tolerance test; LH = luteinizing hormone; RIA = radioimmunoassay; SAH = subarachnoid hemorrhage; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; UCLA = University of California at Los Angeles.

vascular supply.^{17,45} Autopsy reports published more than 30 years ago showed that up to one third of fatally head injured patients sustained anterior pituitary gland necrosis.^{12,16,45} Despite these studies and numerous case reports of patients with posttraumatic hypopituitarism,^{8,24,25,29,33,44,48,49,52} prospective cohort studies of trauma-induced pituitary failure have never been performed. Reports on pituitary dysfunction after aneurysmal SAH are even more limited and have only contained descriptions of the direct mechanical effects of an aneurysm compressing the pituitary gland;²⁷ the effects of the SAH per se on pituitary function have never been studied. Consequently, the rate, risk factors, and clinical significance of neuroendocrine deficits after head injury and SAH are unknown.

Of particular interest is the observation that the chronic neurobehavioral problems and quality of life complaints that plague many patients with head injury^{34,46,56} or SAH^{37,65} are often strikingly similar to those of patients who have adult-onset hypothyroidism, hypoadrenalism,

TABLE 1
Comparison of head-injured patients and healthy volunteers*

Factor	Head-Injured Patients (total 22)	Healthy Volunteers (total 18)
age (yrs) at time of testing	31 ± 10	33 ± 9
sex (female/male ratio)	4:18	4:14
BMI (kg/m ²)	25.1 ± 6.5	25.7 ± 3.9

* Age and BMI values are expressed as the means ± 6 standard deviation.

hypogonadism, and GH deficiency.^{1,3,5,13,18,53,59,66} Endocrinopathy, however, is rarely considered a potential cause of these problems and, instead, the primary brain injury and secondary cerebral insults are typically blamed. This alternative neuroendocrine explanation, either as a primary factor or a factor coexisting with the residual effects of the brain injury, may be relevant to many victims of head injury or SAH, given that hypopituitarism-related neurobehavioral problems are generally improved with hormone therapy.^{5,7,10,53,66}

In this preliminary study, we sought to determine the rate and risk factors of chronic pituitary dysfunction after head injury, and included the results of the first two patients with aneurysmal SAH who were studied. It was hypothesized that the most common deficiencies would be of the somatotroph and gonadotroph axes, given that these cells are known to be particularly vulnerable to a variety of insults, including pituitary apoplexy, irradiation, and trauma.^{24,47,58,66} It was also hypothesized that injury severity, as measured by the patient's initial neurological status, CT findings, and secondary cerebral insults, would correlate with the extent of hormonal failure. To address these hypotheses, patients who were in the chronic phase after head injury or SAH underwent pituitary function testing and the results were compared with those of a healthy age-, sex-, and BMI-matched control group. Patients with and without hypopituitarism were compared in terms of injury-specific and patient-specific factors to determine risk factors for pituitary dysfunction.

Clinical Material and Methods

This protocol was reviewed and approved by the investigational review boards of both the UCLA Medical Center and the Harbor-UCLA Medical Center (Research and Education Institute), and by the National Institutes of Health-funded GCRCs of both institutions.

Eligible patients included adult head-injured patients admitted to UCLA or Harbor-UCLA Medical Centers within 48 hours after injury, who had sustained a closed or penetrating injury that was deemed moderate or severe by GCS criteria (postresuscitation GCS Scores 3–12 or GCS Scores 13–15 in cases in which abnormalities were demonstrated on the CT scan). With the exception of two patients injured in 1976 and in 1985, all patients were treated in accordance with both a Level I trauma center protocol and the "Guidelines for the management of severe head injury."⁹ Management of patients with an aneurysmal SAH is discussed later in *Results*. To avoid the confounding effect of aging, patients older than 60 years of age were not included, because after age 55 years, se-

cretion of GH decreases, resulting in lower average GH and IGF-I levels,³⁹ and because gonadal steroid levels also decrease with aging.^{13,43}

Patient Demographics

Over the last 18 months, 22 patients with head injuries, two patients with aneurysmal SAHs, and 18 healthy volunteers underwent pituitary function testing. The 18 male and four female head-injured patients ranged in age from 16 to 52 years (mean 28 ± 10 years) at the time of injury and from 20 to 52 years (mean 31 ± 10 years) at the time of pituitary function testing; the patients' initial GCS scores ranged from 3 to 15. They were well matched to the control group in terms of age, sex, and BMI (Table 1). Patients were studied from 3 months to 23 years after injury, with the median interval between injury and study being 26 months; eight patients were studied within 3 to 7 months after injury, 12 were studied between 17 months and 5 years after injury, and two were studied at 15 and 23 years postinjury. Fourteen of the 22 patients were enrolled in observational studies in either a previous (1992–1996) or ongoing (1998 to 2002) UCLA Brain Injury Research Center program project.

Healthy Volunteers

A control group was recruited, composed of 18 healthy age-, sex-, and BMI (weight/height²)-matched individuals. Age and BMI were matched within 3 years and within 2 units, respectively. The control group was considered necessary to establish normal reference ranges for pituitary stimulation tests performed for this study and for the specific hormone assays previously validated at the Harbor-UCLA GCRC Core Laboratory.

Risk Factors of Chronic Pituitary Dysfunction and Outcome

The following factors were analyzed: patient age, sex, initial postresuscitation GCS⁶⁴ score, pupillary reactivity, presence of hypotension (systolic blood pressure < 90 mm Hg) or hypoxia (PaO₂ < 60 mm Hg) within 24 hours after injury, the presence of early DI, and the presence of major pathological findings on the first two CT scans had been obtained. These diagnoses included perimesencephalic cistern effacement, diffuse swelling, diffuse swelling with a midline shift greater than 4 mm, diffuse injury with punctate hemorrhages, SAH, evacuated mass lesions (epidural, subdural, and/or intracerebral hematomas), multiple contusions, and gunshot wounds. The severity of ICP and reduced CPP were determined by collecting hourly measurements of ICP and CPP and by computing the mean daily values and the number of hours during which ICP was higher than 20 mm Hg and CPP was lower than 70 mm Hg for each patient. Long-term outcome was defined using the GOS.⁴¹ For the two patients with aneurysmal SAH, aneurysm location, Hunt and Hess clinical grade,³⁶ Fisher SAH grade,²⁸ and presence or absence of vasospasm or hydrocephalus were recorded.

Pituitary Function Testing

Anterior Pituitary Function Tests. Because anterior pituitary dysfunction is most accurately diagnosed using dy-

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dynamic pituitary testing, such testing was implemented in this study.^{35,66} The following tests were performed: 1) an ITT to assess corticotroph and somatotroph secretion by measuring cortisol and GH levels, respectively; 2) a TRH stimulation test to assess levels of TSH and lactotroph (prolactin) response; and 3) a GnRH stimulation test to assess gonadotroph function, by measuring LH and FSH. All patients and volunteers were tested in the GCRC at either Harbor-UCLA or UCLA Medical Center between 8 a.m. and 12 noon after an overnight fast. Blood was drawn 30 minutes before (–30 minutes) and at the time of dynamic pituitary testing (0 minutes) to obtain baseline values, as well as every 30 minutes after testing for the next 2 hours (Table 2). For the thyrotroph and gonadotroph tests, 500 µg TRH and 100 µg GnRH were administered intravenously at Time 0. For the ITT, 0.1 U/kg insulin was administered in an intravenous push at Time 0 to induce a fall in the blood glucose level to 40 mg/dl or less. Additional insulin (0.025 U/kg) was given if this level was not reached within 30 minutes and if the patient did not demonstrate symptoms of hypoglycemia. The risk of marked hypoglycemia was minimized by confirming that patients had a normal concentration of serum glucose prior to insulin injection and by having a 50% glucose solution at bedside. As a prescreening measure for the ITT, within 1 week before undergoing ITT, patients and volunteers underwent testing to measure fasting glucose and cortisol levels, as well as the level of anticonvulsant medication if the patient was receiving it. If a patient had experienced seizures in the past and was receiving anticonvulsant medication, therapeutic levels were confirmed before the ITT commenced.

Posterior Pituitary Function Assessment. At Time 0, the following measurements were collected: serum sodium, blood urea nitrogen, creatinine, osmolality, and AVP, as well as urine osmolality and specific gravity. Normal range values are as follows: serum sodium 135 to 145 mmol/L, blood urea nitrogen 8 to 25 mg/dl, creatinine 0.5 to 1.7 mg/dl, osmolality 270 to 290 mOsm/kg, urine osmolality 500 to 800 mOsm/kg, and specific gravity greater than 1.005.

Hormone Assay Procedures. With the exception of tests for serum ACTH, TSH, AVP, and thyroxine, all hormone assays were performed at the Harbor-UCLA GCRC Core Laboratory. Serum cortisol was measured using RIA kits; the normal morning range is 5 to 21 µg/dl and the normal evening range is 2 to 11 µg/dl. Serum GH was measured using a time-resolved immunofluorometric assay; the normal adult fasting level is 0.1 to 3 ng/ml. Serum IGF-I was measured using RIA kits after acid/ethanol extraction of serum; normal adult ranges are 182 to 780, 114 to 492, and 90 to 360 ng/ml for persons 16 to 24, 25 to 39, and 40 to 54 years of age, respectively. Serum total thyroxine was measured using an RIA kit; the normal adult range is 5.3 to 11.4 µg/dl. Serum FSH and LH were measured using fluoroimmunoassays. Normal adult male ranges are 1 to 8.1 U/L for LH and 1 to 6.9 U/L for FSH. For women, the normal LH increase after GnRH is at least 10 mIU/ml. Serum prolactin was measured using an RIA; the normal range is 1.6 to 21.1 ng/ml. Serum testosterone was measured using a different RIA after extraction; the normal adult male range is 298 to 1043 ng/dl. Serum estradi-

TABLE 2
Schedule for drawing blood to test hormone levels in anterior pituitary function testing

Hormone Tested	Timing W/ Respect to Dynamic Pituitary Testing*					
	–30 Mins	0 Mins	30 Mins	60 Mins	90 Mins	120 Mins
GH	+	+	+	+	+	+
IGF-I		+				
cortisol	+	+	+	+	+	+
TSH	+	+	+	+		
thyroxine		+				
LH & FSH	+	+	+	+	+	+
prolactin	+	+	+	+		
estradiol (women)		+				
testosterone (men)		+				

* See *Anterior Pituitary Function Tests* for details.

ol was measured using a direct assay without extraction; the normal adult female range during the early follicular phase is 20 to 150 pg/ml. Plasma ACTH, AVP, and serum TSH were sent to the Nichols Institute (San Juan Capistrano, CA) for testing. Plasma ACTH was measured using an immunoradiometric assay; the normal adult range in the morning is 9 to 52 ng/ml. Plasma AVP was measured using an RIA after extraction; the normal range is 1 to 13.3 pg/ml. Serum TSH was measured using an immunochromoluminescence assay; the normal adult range is 0.4 to 4.2 mU/L.

Statistical Analysis

Computing the Normal Range. Because hormone variables have a log-normal distribution, determination of normal ranges from the control group was based on the mean and the variance of the log-transformed data. The 95% confidence limit for the mean of the log data at multiple time points (0–120 minutes) and for the area under the curve was determined. Values were transformed back to their original units to define the normal range for each variable. Values for LH and FSH were analyzed separately for men and women, and were further subdivided for pre- and postmenopausal women. Because there was an insufficient number of women in the control group (total of four) for a statistically valid comparison, the determination of whether the gonadotroph responses of the four women with head injuries and the two patients with SAH were normal, was based on established normal ranges for LH, FSH, and estradiol levels.

Rate of Hypopituitarism. Each individual patient's response for a given hormonal axis was compared with the normal range. Responses were declared insufficient in a given pituitary axis if the area-under-the-curve value determined from 0 to 120 minutes fell below the normal control range. The overall rate of dysfunction for each axis was calculated on the basis of these criteria.

Between-group analyses of continuous variables were assessed using Student's t-test. Percentage comparisons were made with Fisher's exact test. All variances are expressed as standard deviations.

Sources of Supplies and Equipment

Serum cortisol concentrations were measured using an

TABLE 3
Summary of patients with pituitary dysfunction*

Case No.	Age (yrs), Sex†	Deficiency‡	Interval§	GCS Score	GOS Score	CT Diagnosis	Pupils	Hypotension	Hypoxia	Mean ICP (mm Hg)	Hrs ICP >20 mm Hg
1	25, M	FSH	61	10	4	DSWS, GSW, ICH, SAH	normal	no	no	18	5
2	24, M	LH, FSH	30	3	3	DS, SDH, EDH, SAH	normal	yes	no	15	10
3	27, M	LH, FSH	31	8	4	DSWS, SDH, SAH, MCx, DIPH, Fx	abn	no	yes	17	70
4	18, M	LH, FSH	178	6	3	DS, MCx	abn	yes	yes	—	—
5	21, M	GH	35	8	5	DSWS, DIPH, Cx, bas Fx**	abn	no	yes	9	0
6	27, F	GH, LH	7	7	4	DSWS, EDH, SAH, bas Fx	abn	yes	yes	15	9
7	22, M	GH, cortisol††	5	5	3	DSWS, SDH, MCx, Fx	abn	yes	yes	18	42
8	34, M	GH, TSH	5	4	3	DS, SAH, MCx, Fx	abn	no	yes	18	122

* Abn = abnormally reactive; bas Fx = basilar skull fracture; Cx = contusion; DIPH = diffuse injury with punctate hemorrhages; DS = diffuse swelling (no shift); DSWS = diffuse swelling with shift; EDH = epidural hematoma; Fx = skull fracture; GSW = gunshot wound; ICH = intracerebral hematoma; MCx = multiple contusions; SDH = subdural hematoma; — = ICP was not monitored.

† Age = age at time of head injury.

‡ Deficiency = pituitary axes affected.

§ Interval = months between injury and pituitary function testing.

|| Glasgow Outcome Scale scores: 5 = good recovery; 4 = moderate disability; 3 = severe disability.

** Basilar fracture extended through sella turcica.

†† Borderline cortisol deficiency.

RIA kit manufactured by ICN Biomedicals, Inc. (Costa Mesa, CA) and serum IGF-I levels were measured using an RIA kit obtained from Nichols Institute (San Juan Capistrano, CA). The RIA used to measure serum prolactin levels included reagents purchased from DSL (Webster, TX) and the RIA used to measure serum testosterone levels included reagents obtained from ICN Biomedicals, Inc., which also provided the reagents included in the direct assay of serum estradiol. Monoclonal antibodies used in the immunofluorometric assay performed to measure serum GH levels were obtained from Seradyn (Indianapolis, IN) and Delfia reagents used in the fluoroimmunoassays of serum FSH and LH were provided by Wallac (Gaithersburg, MD).

Results

Rate of Pituitary Dysfunction

Eight head-injured patients (36.4%) had a subnormal response in at least one hormonal axis (Table 3), including five patients (22.7%) with two axes deemed deficient and one patient with GH deficiency and borderline cortisol deficiency (Case 7).

Growth Hormone. Four (18.2%) of 22 patients had an inadequate GH response to the ITT (Cases 5–8). In each of these patients the GH value was below the 95% confidence limit according to area-under-the-curve criteria, and in all four patients the peak GH levels were 5 ng/ml or less (Fig. 1). Ages for these three men and one woman ranged from 21 to 34 years at the time of injury; they were all tested a minimum of 5 months postinjury and all had had initial GCS scores of 8 or less. Each had sustained a hypotensive or hypoxic insult and had diffuse swelling as evidenced on the initial CT scan and at least one abnormally reactive pupil on initial resuscitation.

In two additional patients GH values fell below the lower limit of the control range values, but not the 95% confidence limit, and peak GH values were less than 7.5 ng/ml. These two patients were considered to be borderline

GH deficient and will undergo repeat testing. In a 29-year-old woman studied at 13 months postinjury, the GH values fell below the 95% confidence limit (peak GH of 4.5 ng/ml); however, on retesting at 17 months postinjury, the values had risen into the low normal range with a peak GH value of 9.1 ng/ml. This patient appears to have recovered somatotroph function. Mean IGF-I values were similar among the patients with GH deficiency ($255 \pm 90 \mu\text{g/L}$), patients without GH deficiency ($264 \pm 78 \mu\text{g/L}$), and the healthy volunteers ($264 \pm 62 \mu\text{g/L}$). However, it is known that random IGF-I levels are a poor diagnostic test for adult GH deficiency.³⁵

Corticotroph Function. Corticotroph function did not fall below the 95% confidence limit in any patients after ITT. However, one patient had a borderline response, with cortisol levels at 90 minutes and 120 minutes falling below the 95% confidence limits and a maximum cortisol level of only 10.3 $\mu\text{g/dl}$ (Fig. 2). This patient (Case 7) was also one of four patients with GH deficiency. He was 22 years old at the time of injury and had a GCS score of 5, diffuse swelling, multiple contusions, and a large subdural hematoma that required evacuation. His injury was complicated by hypotension, hypoxia, and a protracted course of intracranial hypertension and hemodynamic instability, requiring vasopressor therapy for 12 days. He remains severely disabled. In light of his pituitary function results 5 months postinjury, his acute postinjury course is, in retrospect, suspicious for manifestations of partial secondary adrenal insufficiency. However, neither cortisol nor ACTH level was measured during the acute postinjury period when the patient required high-dosage vasopressor therapy.

Luteinizing Hormone and FSH. Insufficient responses to the GnRH stimulation test were seen in four (22.2%) of 18 men for gonadotroph function (Fig. 3; Cases 1–4). In three patients both LH and FSH responses were insufficient and in one patient there was an insufficient FSH response, although all of these men had normal serum testosterone levels. One of four female patients (Case 6) dis-

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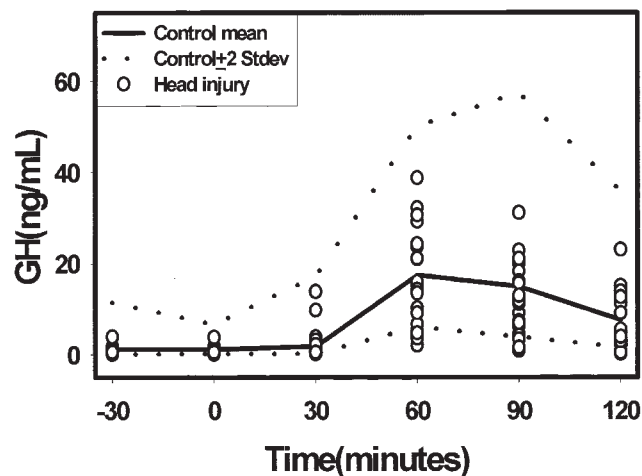


FIG. 1. Time-course graph showing serum GH levels in 22 head-injured patients after insulin administration. All patients had a confirmed serum glucose level of 40 mg/dl or less. In four patients peak GH values were 5 ng/ml or less and in two patients there was a borderline deficiency, with peak values less than 7.5 ng/ml. Stdev = standard deviation.

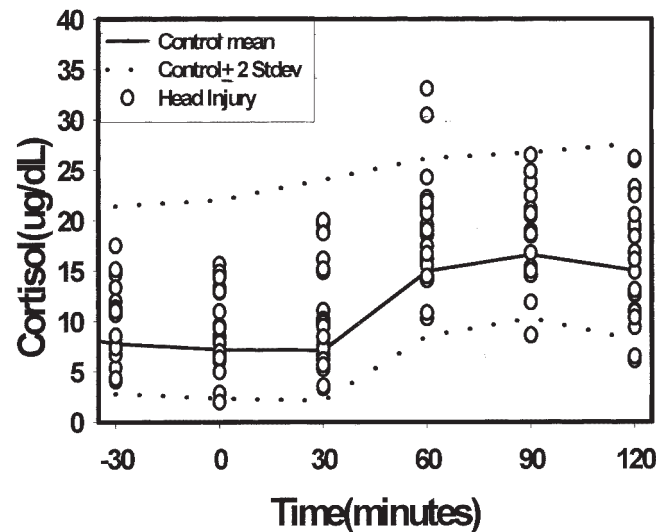


FIG. 2. Time-course graph demonstrating serum cortisol levels in 22 head-injured patients after insulin administration. Only one patient had borderline low values, achieving a maximum cortisol level of 10.3 μ g/dl.

played a subnormal LH response (LH did not increase by > 10 mIU/ml after GnRH administration) with a very low estradiol level (11.6 pg/ml); she is also GH deficient. She continues to have irregular menstrual periods 18 months postinjury and is being given estrogen replacement therapy.

Thyrotroph Function. Only one patient (4.5%) displayed an insufficient rise in TSH in response to the TRH stimulation test (Case 8). This 34-year-old man showed a severely blunted response to TRH (Fig. 4) and thyroxine therapy was initiated approximately 3 months postinjury because of low serum thyroxine and TSH levels. Thyroxine therapy was briefly suspended at 5 months postinjury, at which time the patient was retested but again failed to respond to TRH stimulation. He also has GH deficiency. Similar to the patient with borderline corticotroph function described earlier, this patient sustained a severe injury (initial GCS Score 4), was hypoxic in the field, and had nonreactive pupils, diffuse swelling, and multiple contusions, as demonstrated on the CT scan. He also had a protracted course of intracranial hypertension and difficulty maintaining CPP, requiring vasopressor therapy for 16 days. This patient remains severely disabled.

Lactotroph and Posterior Pituitary Function. In no patient was there an abnormal rise or insufficient response of prolactin to TRH stimulation and there was no evidence of DI in any patient based on nondynamic testing (data not shown).

Predictors of Pituitary Dysfunction

The median GCS score of patients with and without pituitary dysfunction was 7 and there were no significant differences between groups in age or sex distribution. However, none of the three patients with an initial GCS score of 13 to 15 had pituitary dysfunction. Of those with a moderate or severe head injury (initial GCS Score \leq

12), eight (42.1%) of 19 patients displayed an abnormal response in at least one hormonal axis. As shown in Fig. 5, in all eight patients with pituitary dysfunction diffuse swelling was apparent on the CT scan ($p < 0.05$) and seven of these eight patients had sustained a hypotensive and/or hypoxic insult ($p = 0.07$, statistical trend). In no patient with pituitary dysfunction was a hemorrhagic hypothalamic injury observed on the CT scan, although swelling did extend into the hypothalamic region in all eight patients, as evidenced by a compressed third ventricle. The severity of raised ICP and reduced CPP was not significantly different between patients with and without hypopituitarism. However, the two patients with the most severe brain injuries and the most serious hormonal deficiencies (Cases 7 and 8) both had ICP levels greater than 20 mm Hg sustained for more than 40 hours, and CPP levels less than 70 mm Hg for more than 50 hours. Skull fractures and evacuated hematomas occurred with relatively equal frequency among patients with and without pituitary dysfunction. However, one patient with a GH deficiency had a basilar skull fracture extending through the sella turcica (Case 5). The one patient in the series who had sustained a cranial gunshot wound had gonadotroph (FSH) deficiency. Two patients with pituitary dysfunction had urine specific gravities of 1.005 or less on at least one occasion within 1 week of injury, suggestive of mild and transient DI.

Outcomes in Patients With and Without Pituitary Dysfunction

A good recovery (GOS Score 5) was achieved in only one (12.5%) of eight patients with hormone insufficiency compared with nine (64.3%) of 14 patients without hormone insufficiency ($p < 0.05$). Of the 12 patients in the cohort who remained moderately disabled (six patients), severely disabled (five patients), or vegetative (one patient), seven (58.3%) had hypopituitarism.

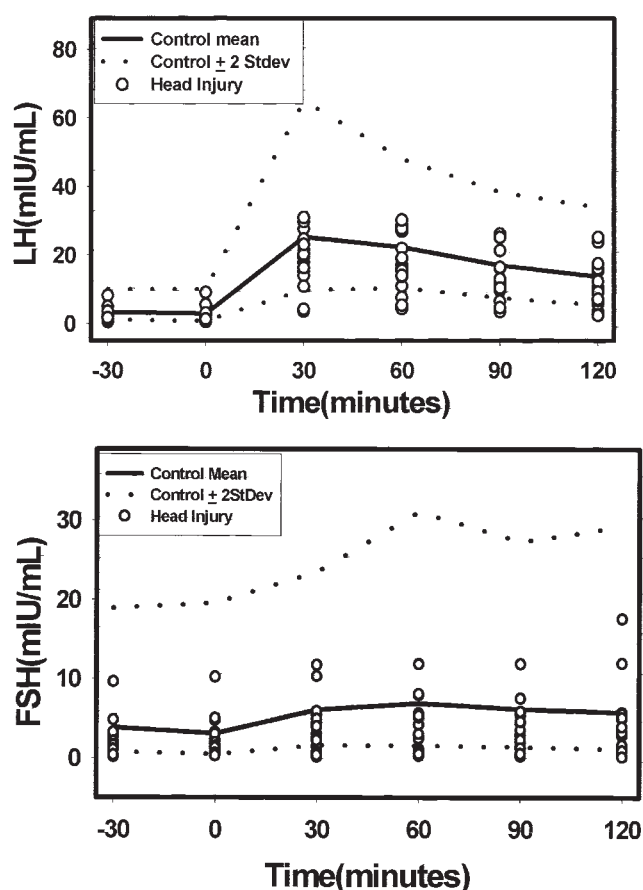


FIG. 3. Time-course graphs showing serum LH (upper) and FSH (lower) levels in 18 head-injured men after GnRH administration. Three men displayed a deficient LH response and four a deficient FSH response. Also note that for both LH and FSH, the majority of patients had values that fell below the mean of the control group.

Hypopituitarism After Aneurysmal SAH

The two patients with aneurysmal SAH were both Hunt and Hess Grade IV with Fisher CT Grade 3 hemorrhages. The first patient, a 52-year-old woman, underwent clipping of an anterior communicating artery aneurysm, was treated for vasospasm with hypervolemia and vasopressor agents, and required a ventriculoperitoneal shunt for hydrocephalus. She remains severely disabled and was tested 13 months after SAH. The second patient, a 29-year-old woman, had a posterior communicating artery aneurysm that was clipped, experienced mild vasospasm, and required two additional craniotomies for temporal lobe swelling. She is moderately disabled, but continues to improve and was tested 3.5 months post-SAH. Both patients are GH deficient according to the ITT criteria, and have peak GH values lower than 5 ng/ml. All other hormonal axes were normal.

Discussion

Summary of Findings

In this preliminary study in which strict biochemical

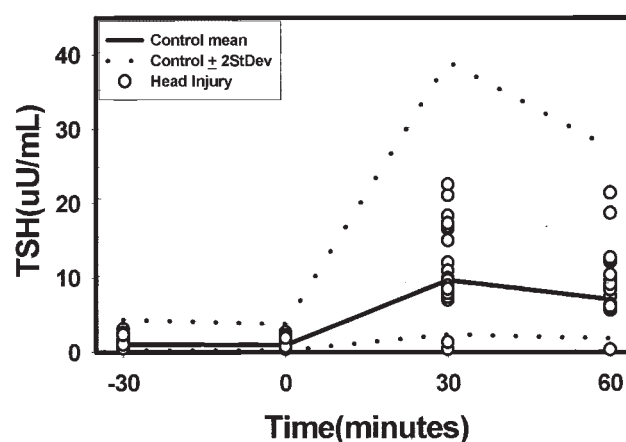


FIG. 4. Time-course graph depicting serum TSH levels ($\mu\text{U}/\text{ml}$) in 22 head-injured patients after TRH administration. Only one patient (Case 8) exhibited an insufficient response to TRH.

criteria were used, long-term pituitary dysfunction was demonstrated in 42% of patients who had sustained a moderate or severe head injury, including decreased GH secretion in 21% of patients. The rate of chronic pituitary dysfunction in the 12 patients who remained vegetative, severely disabled, or moderately disabled was surprisingly high, reaching 58%. Only one of eight patients with hormone insufficiency achieved a good recovery according to GOS criteria. Somatotroph and gonadotroph deficiencies were most common, although the male gonadotroph deficiencies did not result in clinical hypogonadism. Thyrotroph and borderline corticotroph deficiencies were diagnosed in one patient each, both of whom were also GH deficient. These two patients were notable for their severe injuries and poor outcomes. Diffuse brain swelling, hypotensive or hypoxic insults, and a relatively low GCS score were associated with pituitary insufficiency. The two patients with aneurysmal SAH, both Hunt and Hess Grade IV, were diagnosed with GH deficiency. How these findings relate to previous reports of posttraumatic hypopituitarism, the pathophysiological characteristics of pituitary failure, and the potential neurobehavioral significance of hormonal deficiencies are discussed later.

Study Design and Potential Selection Bias

Patients did not undergo pituitary function testing early after injury because previous studies of acute anterior hormone function after head injury have yielded inconsistent results.^{20,32,57} The variability in such studies may relate to the high physiological stress associated with trauma and emergency pharmacological interventions. Regarding the findings of this study, it is acknowledged that the true rate of posttraumatic hypopituitarism may be overestimated because of the small sample size.

Previous Reports on Posttraumatic Hypopituitarism

The relationship between head injury and subsequent pituitary failure was first reported in 1918.¹⁵ Since the 1970s, there have been numerous case reports of both anterior^{8,25,29,38,44,48,52} and posterior^{33,49} pituitary dysfunction occurring posttrauma. Most patients were in comas at

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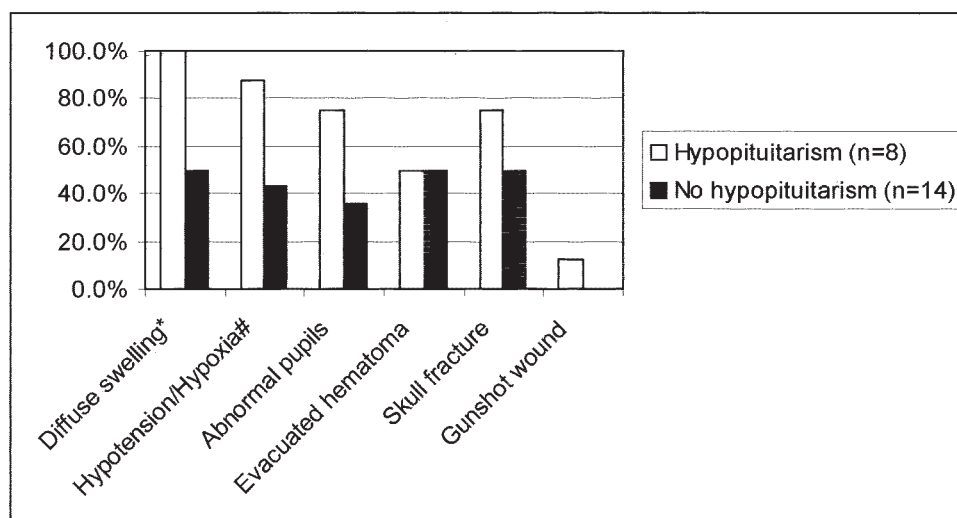


FIG. 5. Bar graph demonstrating the frequency of potential risk factors in patients with and without posttraumatic hypopituitarism. Evidence of diffuse swelling on CT scans ($p < 0.05$, asterisk) and a hypotensive and/or hypoxic insult ($p = 0.07$, pound sign) occurred more frequently in patients in whom hypopituitarism subsequently developed. Although abnormal pupils were also observed more frequently in patients with hypopituitarism, this difference was not significant ($p = 0.18$). n = number of patients.

some point during the acute phase of their injury, but some were unconscious only briefly or had no loss of consciousness.^{24,49} In most instances, pituitary failure appears to be permanent, but, in at least two cases, recovery of function was observed.^{25,38} The largest case series, published in 1986, included a literature review of 53 patients, of whom one third were children.²⁴ Of 20 cases in which detailed endocrinological data were available, the majority had experienced complete anterior gland failure. Specifically, all patients were GH and gonadotropin deficient, 95% were corticotropin deficient, and 85% were thyrotropin deficient. Sixty-two percent of the patients also had increased serum prolactin and 30% suffered permanent DI. In contrast, by assessing a more general population of head-injured patients as was done in the present study, the extent of hormonal dysfunction within patients on average is substantially less. Isolated or combined somatotroph and gonadotroph dysfunctions appear to be most common, whereas corticotroph, thyrotroph, and posterior pituitary deficiencies are uncommon.

Pathophysiology of Posttraumatic Hypopituitarism

In this study, in all patients with pituitary dysfunction, diffuse swelling was apparent on CT scanning and in all except one (with a cranial gunshot wound) there was evidence of a hypotensive or hypoxic insult. The link between posttraumatic hypotension and hypoxia and subsequent brain swelling has been well established clinically²⁶ and likely is relevant to the pathophysiology of traumatic endocrinopathy.

In the 1960s two studies provided descriptions of pituitary lesions after fatal head injury.^{12,45} In these reports, for a total of 202 patients, only 26% of the specimens were normal; 59% contained capsular hemorrhage, 31% had posterior lobe hemorrhage, 17% had stalk hemorrhage, 3% had stalk necrosis, and one specimen had a stalk lac-

eration. Most striking was the finding of anterior lobe necrosis in 22% of patients. In the study conducted by Kornblum and Fisher,⁴⁵ anterior lobe necrosis was observed in 35% of patients who survived longer than 12 hours. This finding was observed only in specimens in which there was accompanying brain and pituitary gland swelling and in individuals whose injuries were complicated by shock. The necrosis pattern always corresponded with the blood supply of the long hypophyseal portal veins. Fed by the superior hypophyseal arteries and other small branches of the circle of Willis, the long portal veins pass through the diaphragma sella, where they are vulnerable to mechanical compression from both brain and pituitary gland swelling and direct stalk injury.^{2,16,17,45} They provide the anterior lobe with 70 to 90% of its blood supply, predominantly in its lateral aspects. In contrast, the short hypophyseal portal veins arise below the diaphragma sella and supply the anterior lobe with less than 30% of its blood supply, mostly in the medial portion, and they supply the posterior lobe.^{2,4,31}

Because somatotrophs are located primarily in the lateral wings of the anterior lobe and gonadotrophs are found in the pars distalis and pars tuberalis, the majority of these two cell groups are located in the vulnerable vascular territory of the long hypophyseal portal system. In contrast, corticotrophs and thyrotrophs are largely found in the anteromedial portion of the gland,⁴ and thereby, in the more protected territory of the short hypophyseal portal system. This anatomical arrangement appears to translate into a hierarchy of hormone failure that holds true not only for head injury,²⁴ but also for pituitary apoplexy, surgery, and pituitary irradiation.^{47,58,66}

Other mechanisms for traumatic hypopituitarism include direct mechanical injury to the pituitary gland, the stalk, or the hypothalamus. In this study, one patient had a fracture that passed through the sella and may have been a factor in the development of GH deficiency in that case.

Previous reports have also identified sellar fractures in association with hypopituitarism.^{8,16} None of the patients with hypopituitarism in this study experienced acute or chronic DI, suggesting a direct stalk injury, but such cases have been reported.^{33,49} Although hypothalamic injuries could theoretically lead to hypopituitarism, most individuals who sustain a major hypothalamic injury probably die.¹⁴ Based on the findings of this study and those of previous postmortem studies, a vascular insult may be the most common cause of posttraumatic hypopituitarism.^{17,45} The pathophysiological characteristics are similar to those of postpartum pituitary necrosis (Sheehan syndrome), which is also a primary vascular event resulting from major hemorrhage and hypotension.⁶¹ Whether endogenous catecholamine or vasopressor therapy exacerbates pituitary hypoperfusion after head injury, as is postulated to occur in Sheehan syndrome, warrants further study.⁶¹

Neurobehavioral Impacts of Hypopituitarism and Hormone Replacement Therapy

The significance of the association between chronic pituitary dysfunction and poor outcome in this study is unclear. This finding may simply reflect that, in addition to sustaining injuries to their pituitary glands, these patients also had more severe brain injuries than patients with normal pituitary function. However, the possibility that untreated hypopituitarism contributes to the chronic neurobehavioral problems seen in many head-injured patients warrants consideration.^{23,34,46,56} In the few case reports described, hormone-replacement therapy in hormone-deficient head-injured patients resulted in major neurobehavioral improvements.^{24,44} The effects of acquired thyrotropin and corticotropin deficiencies have long been appreciated and replacement therapy is considered essential and highly beneficial for these hormone-deficient individuals.^{1,5,53,66}

Growth Hormone

Adult GH deficiency has been linked to impairments in memory, perceptual and motor skills, intelligence quotient, higher anxiety levels, and a lower quality of life.^{10,18,19,51,59} In several placebo-controlled studies of GH-deficient patients who did not sustain brain injury, beneficial effects of GH replacement included improved attention and cognition, comprehension and vocabulary, energy level and mood, sense of well being, and reductions in depressive symptoms, anxiety, and fearfulness.^{7,10,51,62} Enhanced quality of life after GH therapy has also been demonstrated.^{30,54} However, one placebo-controlled study showed no effect of GH therapy on cognitive function and quality of life.⁶ The beneficial effects of GH have been postulated to be, in part, attributable to its easy passage into the central nervous system and its favorable effect on brain thyroxine levels.¹¹ Growth hormone's second messenger, IGF-I, also appears to play a key role in brain development and enhances early recovery after experimental brain injury.^{21,60} The neurobehavioral effects of physiological GH replacement in GH-deficient patients with head injury remain unknown. Other effects of GH replacement that might be beneficial to head-injured patients include increased muscle mass⁴² and enhanced exercise capacity and cardiac function.⁵⁵ Based on the findings

of the present study in which four patients were shown to be GH deficient and had residual neurobehavioral problems potentially attributable to GH deficiency, a placebo-controlled GH replacement study is being planned.

Androgens and Estrogens

Testosterone deficiency has been associated with impaired neurobehavioral function, particularly verbal fluency and mood disturbance,^{3,63,67} both of which are improved by hormone replacement. Testosterone replacement therapy in men also improves sexual function, libido, muscle mass, and bone formation.^{63,68} Similarly, in women, cognitive function and memory appear to be impaired by low estrogen levels and conversely, estrogen replacement is associated with enhanced neurocognitive performance.^{13,40} Although in the present study, all four men exhibiting a subnormal LH or FSH response had normal serum testosterone levels, there have been numerous cases of clinical hypogonadism reported after head injury.^{8,24,44} These men may be at risk of future hypogonadism and will be closely followed. The one woman in this study with LH and estradiol deficiency is receiving estrogen therapy.

Hypopituitarism After Aneurysmal SAH

Few conclusions can be drawn regarding the rate and risk factors of hormonal insufficiency after SAH by analyzing two patients. Both women were Hunt and Hess Grade IV and had complicated clinical courses that may have contributed to the development of GH deficiency. Clearly aneurysmal SAH poses risk to the pituitary gland and stalk, given the proximity of these structures to circle of Willis vessels and the potential for vasospasm of the feeding branches to the hypophyseal vasculature. Further study is needed to determine the relative importance of factors such as aneurysm location, clinical grade, vasospasm, hydrocephalus, and whether an aneurysm is clipped surgically or coils are placed by an endovascular procedure. Given that a majority of patients with SAH have persistent neurobehavioral and quality-of-life problems,⁶⁵ the search for a treatable cause of these impairments such as GH deficiency warrants further study. It is notable that no consistent relationship exists between the site of aneurysm rupture and the nature of the neurocognitive deficits that occur after SAH.^{22,37,50,65} A more global neurobehavioral derangement, such as that which can occur with GH deficiency, might explain these discrepant findings in at least some patients.

Conclusions

Pituitary dysfunction appears to be a common phenomenon after head injury and also occurs in patients with poor-grade aneurysms. In this preliminary report we suggest that approximately 40% of victims suffering from moderate and severe head injury will develop some degree of long-term anterior pituitary gland dysfunction, with GH deficiency and gonadotroph dysfunction being most common and thyrotroph or corticotroph deficiencies being uncommon. Although in a few instances direct mechanical trauma to the gland may result in hypopituitarism, it is postulated that, in most cases, a vascular insult is the primary cause. Given the large numbers of indi-

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viduals who have suffered or will suffer a serious head injury or SAH, the neurobehavioral impact of hypopituitarism after such insults is likely significant. Further study is needed, however, to define more clearly the risk factors for pituitary dysfunction and the benefits of hormone-replacement therapy. Based on our initial findings, pituitary function testing is probably warranted in most patients with moderate or severe head injury, particularly those who sustain hypotensive or hypoxic insults, those in whom there is evidence of diffuse brain swelling on CT scans, and those patients with basilar skull fractures that pass through the sella turcica. These findings are particularly relevant for children with head injuries, given that growth and development are so dependent on optimum hormonal functioning.

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