Evidence for Integrity of the Growth Hormone/Insulin-Like Growth Factor-1 Axis in Patients With Severe Head Trauma During Rehabilitation

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Severe traumatic head injury has been recognized to be associated with hypothalamo-hypophyseal impairment and subsequent abnormalities in hormone secretion, which can contribute to a prolonged clinical course and to hampered recovery in many head-injured patients. Most of the data on the growth hormone/insulin-like growth factor -1 (GH/IGF-1) axis function have been obtained early after head injury, whereas GH secretory pattern has not been fully elucidated after patients had left the intensive care unit. We examined the activity of the GH/IGF-1 axis in 16 severely closed head-injured (CHI) patients (14 males; age range, 17 to 47 years; body mass index [BMI], 21.4 ± 0.8 kg/m^2) during the rehabilitation period at least 1 month after leaving the intensive care unit and in 12 sex-, age-, and weight-matched healthy controls. The severity of trauma was assessed by the Glasgow Coma Scale (GCS) score (8 or less), posttraumatic amnesia (PTA, more than 24 hours), and initial computed tomography (CT) scan. The clinical picture at time of the study was evaluated by the Rancho Los Amigos Scale of Cognitive Functioning (CFS) and the Functional Independence Measure (FIM). In all subjects, we evaluated basal levels of anterior pituitary hormones, IGF-1, insulin-like growth factor-binding protein (IGFBP)-3, and IGFBP-1, as well as the GH responses to intravenous (IV) infusion of growth hormone-releasing hormone (GHRH) alone, GHRH plus arginine (ARG), and the GH release evoked by somatostatin (SRIH) infusion withdrawal, which is related to endogenous GHRH tone. In all subjects, nutritional parameters and nitrogen balance were normal. Basal plasma concentrations of GH, IGF-1, IGFBP-3, and IGFBP-1 did not significantly differ between CHI patients and controls. The GH responses to GHRH and GHRH plus ARG did not significantly differ between CHI patients (GH peak, 10.7 ± 3.0 μg/L; area under the curve [AUC], 5.9 ± 1.5 μg/L · min; and GH peak, 34.7 ± 6.1 μg/L; AUC, 20.25 ± 3.3 μg/L · min, respectively) and normal subjects (GH peak at 30 minutes, 7.23 ± 1.35 μg/L; AUC, 4.7 ± 0.8 μg/L · min; and GH peak at 60 minutes, 41.0 ± 5.1 μg/L; AUC, 24.3 ± 1.7 μg/L · min, respectively). SRIH withdrawal resulted in an unequivocal increase in plasma GH concentrations both in CHI patients and in controls, without any significant difference between the 2 groups. A negative correlation was found between the GH response (ΔGH peak) to SRIH withdrawal and CFS ($r = -.615$, $P < .005$). In conclusion, our study indicates that patients receiving rehabilitation after leaving the intensive care unit for severe traumatic head injury have no significant changes of GH secretion with normal central regulation of the GH-IGF-1 axis.

SEVERE TRAUMATIC HEAD injury has been recognized to be associated with hypothalamo-hypophyseal impairment and subsequent abnormalities in hormone secretion, which can contribute to a prolonged clinical course with metabolic dysfunction and to a delayed or hampered recovery in many head-injured patients.[1-5]

The importance of growth hormone/insulin-like growth factor (GH/IGF-1) axis for metabolic homeostasis and cellular biochemical pathways during critical illness is well known.[6,7] Most of the data on the function of the somatotroph axis in head-injured patients has been obtained, however, early after injury.

In the acute phase of head trauma, low[8,9] or high[10-12] basal circulating GH levels associated with low IGF-1 concentrations have been shown. A decrease in the frequency of GH bursts and in the difference between day/nighttime secretory spikes have been detected 24 to 48 hours after severe trauma, suggesting that a relative hyposomatotropinism may participate in the pathogenesis of the wasting syndrome of this phase of illness.[13] Moreover, a paradoxical GH response to thyrotropin-releasing hormone (TRH) on the first day with a progressive increase in the GH response to growth hormone-releasing hormone (GHRH) from day 2 to day 15 after head injury have been observed, demonstrating an imbalance of the complex neuroendocrine system controlling GH secretion.[11]

On the contrary, the secretory pattern of GH has not been fully elucidated in head-injured patients once they leave the intensive care unit. Defining GH profile may be of potential relevance in these patients. In fact, awareness of the possible alterations in the somatotroph axis could be helpful for clarifying pathophysiologic mechanisms underlying the metabolic derangement present in the chronic phase of illness and whether endocrine intervention may be needed to accelerate recovery.

Therefore, the purpose of the present study was to examine the activity of the GH/IGF-1 axis in a group of carefully selected severely closed head-injured (CHI) patients during the rehabilitation period at least 1 month after leaving the intensive care unit. The integrity of hypothalamo-pituitary function was assessed by determining the GH responses to GHRH and GHRH plus arginine (ARG), and by evaluating the GH release evoked by withdrawal of somatostatin (SRIH) infusion that is related to endogenous GHRH tone.[14,15] The correlation be-

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tween the function of GH axis and the overall severity and outcome of trauma was also evaluated.

SUBJECTS AND METHODS

Subjects

Sixteen CHI patients (2 females, 14 males) age, 17 to 47 years (mean, 31.6 ± 2.7 years) and 12 healthy volunteers (2 females, 10 males) age, 19 to 45 years (mean, 33.1 ± 2.9 years) were recruited to participate in this study. The body mass index (BMI) ranged from 18.0 to 26.5 kg/m^2 (mean, 21.4 ± 0.8 kg/m^2) in CHI patients and from 18.9 to 26.5 kg/m^2 (mean, 22.7 ± 0.6 kg/m^2) in healthy subjects.

Patients were studied during the rehabilitation period at least 1 month after leaving the intensive care unit for severe traumatic brain injury. Rehabilitation consisted of an intensive inpatient rehabilitation program typically designed for patients transferred from acute hospital care, who are medically stable and able to tolerate a minimum of 3 hours of therapeutic intervention per day, 5 days per week. The program included treatment and management by an interdisciplinary treatment team, with an emphasis on functional recovery and community reintegration.

The severity of the trauma was assessed using the Glasgow Coma Scale (GCS) score (severe head injury was defined as a postresuscitation GSC score of 8 or less).[16] The patients' initial GCS scores ranged from 3 to 8 (mean, 5.5 ± 0.4). All patients had loss of memory for events immediately before or after the accident, with posttraumatic amnesia (PTA) for more than 24 hours. Eleven patients (68.8%) had multiple trauma lesions (bone fractures in 9 patients, bone fractures and thoracic trauma in 1 patient, and abdominal trauma in 1 patient); 7 patients had undergone neurosurgical procedures. The type of head injury was characterized by computed tomography (CT) scan according to Marshall's classification[17]: diffuse injury I (no visible pathology); diffuse injury II (cisterns present with midline shift 0 to 5 mm and/or no large lesion greater than 25 cc); diffuse injury III (diffuse brain swelling, cisterns compressed with midline shift 0 to 5 mm, no large lesion greater than 25 cc); diffuse injury IV (midline shift greater than 5 mm, no large lesion greater than 25 cc); evacuated mass lesion (any lesion surgically evacuated); nonevacuated mass lesion (lesion more than 25 cc). The clinical picture at time of the study was evaluated by: (1) the Rancho Los Amigos Scale of Cognitive Functioning (CFS), which is divided into 8 levels communicating the patient's cognitive level[18]; (2) the Functional Independence Measure (FIM), an 18-item 7 level functional assessment scale that evaluates the amount of assistance required by a person with a disability to perform basic daily activities safely and effectively. Each of the 18 items has a maximum score of 7 and the lowest score on each is 1. Total scores can range from 18 to 126.[19] All clinical data are listed in Table 1.

Criteria for patients' exclusion were as follows: patients younger than 17 years or older than 50 years of age; patients with a history of preexisting metabolic, endocrine, neurologic, cardiac or pulmonary diseases; patients with liver or renal failure, or infectious diseases; patients treated with barbiturates, or receiving medications that could affect GH secretion; patients requiring corticosteroid treatment during the last 2 months. Moreover, we did not include subjects with resting blood pressure ≤ 120/70 mm Hg and patients receiving parenteral nutrition and/or mechanical ventilation.

Patients were receiving enteral or oral nutrition, which consisted of a caloric intake of 30 to 35 kcal/kg/d, with 1.2 to 1.4 g/kg/d of protein intake and a caloric/nitrogen ratio of 134:1. The diet and the mixture for enteral nutrition (Nutrison Energy Multi Fiber; Nutricia, Milan, Italy) contained 16% protein, 49% carbohydrate, and 35% lipid. No ARG and/or glutamine supplements were administered. Nitrogen balance was calculated as the difference between nitrogen intake (g protein ingested/6.25) and nitrogen output (24-hour urine collection for urea nitrogen + 4). Control subjects were given oral rather than enteral nutrition, as it did not seem ethical to place feeding lines in normal subjects. The study protocol was approved by the Ethical Committee of the University of Ferrara. Informed consent was obtained from subjects or next of kin.

Experimental Procedures

The use of alcohol, tea, and caffeine-containing food was prohibited. After an overnight fast, an indwelling intravenous (IV) cannula was inserted in both forearms at 7:30 AM and kept open with a slow infusion of 0.9% saline for separate blood sampling and drug administration. An

Table 1. Clinical Characteristics of the CHI Patients

No. of Patients	Age (yr)	Sex	BMI (kg/m^2)	EI	GCS Score	CT Marshall's Classification	Time After Injury (d)	CFS Level	FIM
1	24	M	20.5	Yes	8	2	50	8	112
2	17	M	19.0	Yes	4	EM	60	3	18
3	33	M	22.2	Yes	5	EM	55	7	18
4	34	M	26.5	Yes	8	3	60	6	18
5	34	M	26.5	No	8	3	120	6	18
6	22	M	18.5	Yes	8	3	150	2	18
7	43	M	20.5	Yes	5	1	50	6	70
8	22	M	22.1	No	4	3	90	2	25
9	40	M	18.9	Yes	3	EM	155	2	18
10	46	M	22.1	Yes	5	4	150	5	28
11	17	M	18.6	Yes	4	4	60	5	19
12	47	M	24.5	Yes	3	EM	85	4	22
13	20	M	18.0	Yes	6	EM	60	3	20
14	47	M	24.5	No	7	2	60	7	49
15	24	F	19.0	No	5	2	90	8	79
16	35	F	24.2	No	5	EM	120	4	40

Abbreviations: BMI, body mass index; EI, extracranial injury; GCS, Glasgow Coma Scale; CT, computed tomography; CFS, Cognitive Functioning Scale (Rancho Los Amigos[18]); FIM, Functional Independence Measures.[19] Marshall's classification[17]: I, no visible pathology; II, cisterns present with midline shift 0 to 5 mm and/or no large lesion greater than 25 cc; III, diffuse brain swelling, cisterns compressed with midline shift 0 to 5 mm, no large lesion greater than 25 cc; IV diffuse injury with midline shift greater than 5 mm, no large lesion greater than 25 cc; EM, evacuated mass.

equilibration period of 1 hour was allowed before baseline blood samples were obtained. Subjects remained supine and awake in bed throughout the procedures, which were attended by a nurse and a physician. At 4-day intervals, each subject was tested on 3 separate occasions in a single blind, randomized manner: (1) IV administration of GHRH alone (Geref, Serono, Milan, Italy, 1 μg/kg bolus) with blood collection at –30 and 0 (before GHRH bolus), 15, 30, 45, 60, 90, and 120 minutes for GH measurements; (2) IV administration of GHRH (Geref, Serono, 1 μg/kg bolus, at time 0) plus infusion of L-ARG hydrochloride (30 g in 60 mL saline infused IV over a 30-minute period from time 0 to 30 minutes of the study), with blood collection at –30 and 0, 15, 30, 45, 60, 90, and 120 minutes for GH measurements; (3) IV infusion of SRIH (Stilamin, Serono) in 50 mL normal saline at a rate of 9 μg/kg/h from time 0 to 90 minutes of the study, with blood collection at –30 and 0, 30, 60, 90, 105, 120, 135, 150, 165, and 180 minutes for GH determinations. All infusions were performed with a volumetric infusion pump (no. 922; IMED, Oxon, United Kingdom).

Baseline plasma levels of IGF-1, insulin-like growth factor-binding protein (IGFBP)-1, IGFBP-3, thyroid-stimulating hormone (TSH), free thyroxine (FT_4), corticotropin (ACTH), cortisol, prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (T) or estradiol (E) were also measured in each subjects at –30 and 0 minutes. Nutritional status was evaluated by serum total protein, albumin, and prealbumin measurements.

Analytical Procedures

Blood samples were drawn into precooled glass tubes containing 1 mg/mL ethylene-diamine tetraacetic acid disodium salt (EDTA-2Na) for hormone determinations. They were promptly centrifuged at 3,000 × *g* for 15 minutes at 4°C, and the plasma was then frozen at –80°C until analysis. All samples for each hormone were processed in duplicate in the same assay.

GH was measured by immunoradiometric assay (IRMA) with reagents supplied by Nichols Institute Diagnostics (San Juan Capistrano, CA). The limit of detection was 0.05 μg/L, with intra- and interassay coefficients of variation (CVs) of 3.3% and 6.1%, respectively. Plasma IGF-1 was determined by radioimmunoassay (RIA) using a commercially available kit (Medgenix Diagnostic S.A, Fleurus, Belgium), after acid-ethanol extraction from EDTA plasma. The sensitivity of the method was 0.015 nmol/L. The intra- and interassay CVs were 9.6 and 6.1%, respectively. IGFBP-1 was measured by IRMA (Diagnostic System Laboratories, Webster, TX). The sensitivity of the method was 0.33 μg/L. The intra- and interassay CVs were 6.3% and 6.1%, respectively. IGFBP-3 was measured by RIA (Nichols Institute Diagnostic). The sensitivity of the method was 0.063 mg/L. The intra- and interassay CVs were 5.3% and 8.0%, respectively.

ACTH was determined by IRMA (Nichols Institute Diagnostics). Cortisol, E, and T were determined by RIA (Diagnostic Products, Los Angeles, CA). LH and FSH were measured with a 2-site chemiluminometric immunoassay (ACS, Ciba Corning Diagnostic, Medfield, MA). PRL, TSH, and FT_4 were measured using an automated chemiluminescence system (ACS, Centaur, Chiron Diagnostics, East Walpole, MA). The intra- and interassay CVs for all methods were less than 5.8% and 7.8%, respectively.

The age-matched range in healthy controls was: IGF-1, 17.5 to 64.4 nmol/L (18 to 30 years), 15.2 to 52.9 nmol/L (31 to 40 years), 12 to 41.6 nmol/L (41 to 50 years); IGFBP-3, 2 to 4.9 mg/L; IGFBP-1, 13 to 73 μg/L; ACTH, 1.5 to 11.5 pmol/L; cortisol, 0.22 to 0.70 μmol/L (8 to 10 AM), TSH, 0.1 to 4.2 mIU/L; FT_4, 10.3 to 19.4 pmol/L; PRL, 0.09 to 0.99 nmol/L in women and 0.05 to 0.72 nmol/L in men; E, 0.074 to 0.555 nmol/L (follicular phase), 0.444 to 1.388 nmol/L (middle phase), 0.111 to 0.962 nmol/L (luteal phase); T, 10.1 to 34.7 nmol/L; LH, 2.5 to 10 U/L (follicular phase), 25 to 70 U/L (middle phase), 1 to 13 U/L (luteal phase) in women; LH, 1 to 10 U/L in men; FSH, 2.5 to 10 U/L (follicular phase), 25 to 70 U/L (middle phase), 0.3 to 2.1 U/L (luteal phase) in women; FSH, 1 to 7 U/L in men.

Total serum protein, albumin, prealbumin, and urinary uric nitrogen were determined by standard methods.

Statistical Analysis

GH plasma concentrations were expressed both as absolute values (μg/L) and as areas under the curves from 0 to 120 minutes (AUC 0 to 120 minutes, μg/L · min) calculated by trapezoidal methods after GHRH and GHRH plus ARG administration. To facilitate comparison of the GH secretory profiles after withdrawal of SRIH infusion, plasma GH responses were also expressed as peak increment in GH (the peak value detected after termination of SRIH infusion minus the mean value of plasma GH obtained during the 90-minute period of SRIH infusion in each subject, ie, ΔGH peak). All results are expressed as the mean ± SEM. The results were compared within each group by using paired Student's *t* test and between groups by 1-way analysis of variance (ANOVA). Multiple comparison between groups was performed by using the Bonferroni test. Correlation between GH level and CSG score, CFS, or FIM were performed with the linear regression analysis. *P* values less than .05 were considered statistically significant. Baseline levels of GH were obtained from the mean (± SEM) of the 2 values determined at times –30 and 0 minutes of the study for all tests.

RESULTS

Basal Values

All subjects showed serum total protein, albumin, and prealbumin in the normal range, without significant differences between CHI patients and normal subjects. Nitrogen balance was in equilibrium in all patients (data not shown).

The mean basal plasma hormone concentrations are reported in Table 2. All CHI patients showed TSH and FT_4 levels in the normal range. Plasma ACTH and cortisol levels were slightly elevated in 7 (43.7%) and in 3 (18.7%) CHI patients, respectively. Plasma PRL concentrations were slightly elevated in 5 (31.2%) patients. Finally, 9 (56.2%) CHI patients (2 females, 7 males) had low levels of E or T associated with low or normal plasma LH and FSH concentrations when compared with age-matched normal range controls.

In CHI patients, baseline levels of GH (1.13 ± 0.23 μg/L) and IGF-1 (29.5 ± 2.7 nmol/L) did not significantly differ from those observed in normal subjects (GH, 1.15 ± 0.10 μg/L; IGF-1, 27.6 ± 3.0 nmol/L). No significant differences in IGFBP-3 and IGFBP-1 levels were found between CHI patients (43.4 ± 5.4 μg/L and 3.6 ± 0.3 mg/L, respectively) and normal subjects (40.5 ± 4.7 μg/L and 3.7 ± 0.3 mg/L, respectively).

GH Responses to Tests

As indicated in Fig 1, GHRH administration caused a significant ($P < .01$) increase in GH levels in both CHI patients (peak, 10.7 ± 3.0 μg/L at 30 minutes) and normal subjects (peak, 7.23 ± 1.35 μg/L at 30 minutes), with no difference between the 2 groups. Similarly, the mean AUC of GHRH-induced GH release did not significantly differ between CHI patients (5.9 ± 1.5 μg/L · min) and controls (4.7 ± 0.8 μg/L · min).

The GH response to GHRH plus ARG is reported in Fig 2. In normal subjects, GHRH plus ARG induced a clear-cut increase in GH concentrations (peak, 41.0 ± 5.1 μg/L at 60 minutes; and AUC 24.3 ± 1.7 μg/L · min), which was signif-

Table 2. Basal Hormonal Evaluation of the CHI Patients

No. of Patients	LH (mU/mL)	FSH (mU/mL)	E (pmol/L)	T (nmol/L)	PRL (nmol/L)	ACTH (pmol/L)	Cortisol (μmol/L)	TSH (IU/mL)	FT_4 (pmol/L)
1	1.9	2.9	ND	15.8	0.38	6.2	0.29	1.68	11.0
2	1.6	0.8	ND	4.9	1.69	9.7	0.66	2.73	14.5
3	3.0	2.7	ND	10.2	1.19	23.3	0.74	3.87	12.0
4	3.0	2.7	ND	20.1	1.19	13.8	0.81	3.87	12.0
5	4.3	3.0	ND	5.4	1.18	7.3	0.41	2.31	12.5
6	2.6	2.5	ND	7.8	0.50	16.1	0.64	0.50	18.9
7	3.6	3.8	ND	17.5	0.55	9.9	0.54	1.10	12.6
8	4.2	4.8	ND	12.2	0.72	15.1	0.63	2.84	15.2
9	1.8	0.4	ND	6.3	0.81	26.6	0.86	1.59	11.6
10	4.2	8.0	ND	7.5	0.72	11.4	0.53	1.16	16.4
11	0.8	6.8	ND	6.2	0.68	11.4	0.52	3.24	12.3
12	3.8	8.9	ND	7.2	1.30	26.4	0.61	2.21	10.3
13	3.1	2.9	ND	15.6	0.49	7.7	0.50	1.30	15.5
14	3.2	2.1	ND	21.7	0.42	7.9	0.40	1.25	15.6
15	1.4	4.2	58.7	ND	0.99	7.3	0.38	2.14	16.9
16	2.0	4.2	14.7	ND	0.32	15.6	0.49	2.65	16.8

Abbreviation: ND, not determined.

icantly ($P < .001$) higher than that observed after GHRH alone (peak, 7.2 ± 1.2 μg/L; AUC, 5.0 ± 0.7 μg/L · min) (Fig 1). Similarly, in CHI patients, GHRH plus ARG induced a clear-cut increase in GH concentrations (peak, 34.7 ± 6.1 μg/L at 45 minutes; AUC, 20.25 ± 3.31 μg/L · min), which was significantly ($P < .001$) higher than that observed after GHRH alone (peak, 10.7 ± 3.0 μg/L; AUC, 5.9 ± 1.5 μg/L · min). No significant differences were observed between normal subjects and CHI patients, either in the peak values or in the AUCs after GHRH plus ARG.

The GH response to SRIH withdrawal is reported in Fig 3. SRIH withdrawal resulted in an unequivocal increase in plasma GH levels both in CHI patients (beginning at 120 minutes up to a maximum of 3.80 ± 1.05 μg/L at 150 minutes) and in normal subjects (beginning at 105 minutes up to a maximum of 3.59 ± 1.00 μg/L at 150 minutes), with no significant difference between the 2 groups. Moreover, the mean ΔGH peak did not significantly differ between CHI patients (4.78 ± 1.02 μg/L) and normal subjects (6.46 ± 1.27 μg/L).

No side effects were observed during GHRH alone, GHRH plus ARG, and SRIH administration either in CHI patients or normal subjects. The individual evaluation of GH/IGF-1 axis function in CHI patients and in normal subjects is summarized in Table 3.

Correlation Between GH Responses to Tests and Clinical Measures of Head Trauma Severity

No significant correlation was observed either between the GH response (AUC) to GHRH, the initial GCS score, CFS, and FIM. No significant correlation was observed between GH response (AUC) to GHRH plus ARG and the initial GCS score, CFS, and FIM. A negative correlation was found between the GH response (ΔGH peak) to SRIH withdrawal and CFS ($r = -.615$, $P < .005$). No significant correlation was observed between GH response (ΔGH peak) to SRIH withdrawal and GCS, CFS, and FIM.

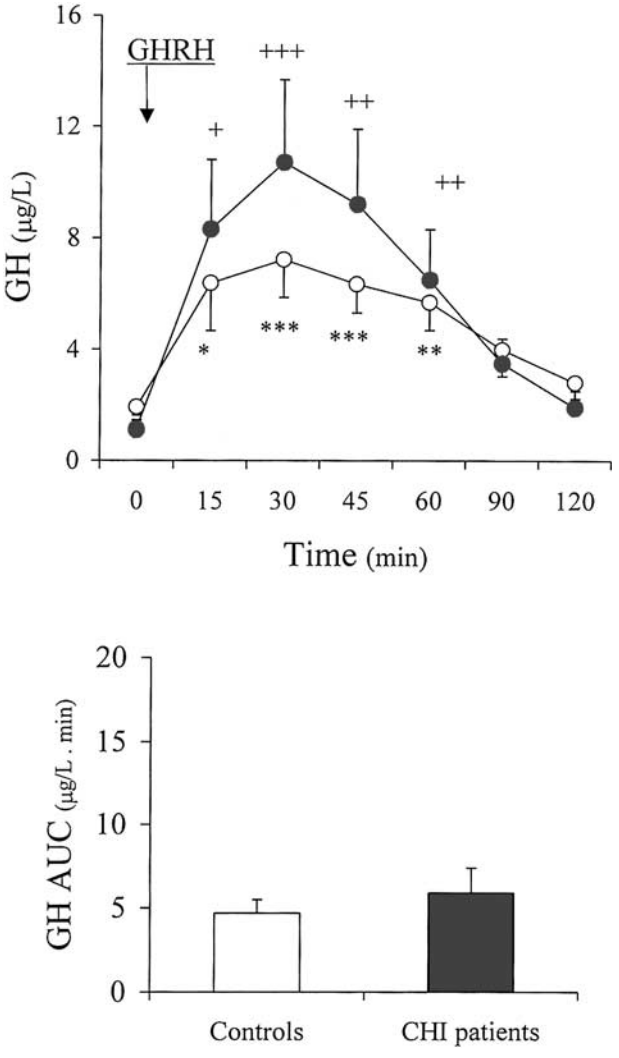

Fig 1. GH response to GHRH in severe CHI patients and normal subjects. *$P < .05$, **$P < .002$, ***$P < .001$ *v* basal (normal subjects). $^{+}P < .05$, $^{++}P < .002$, $^{+++}P < .001$ *v* basal (CHI patients).

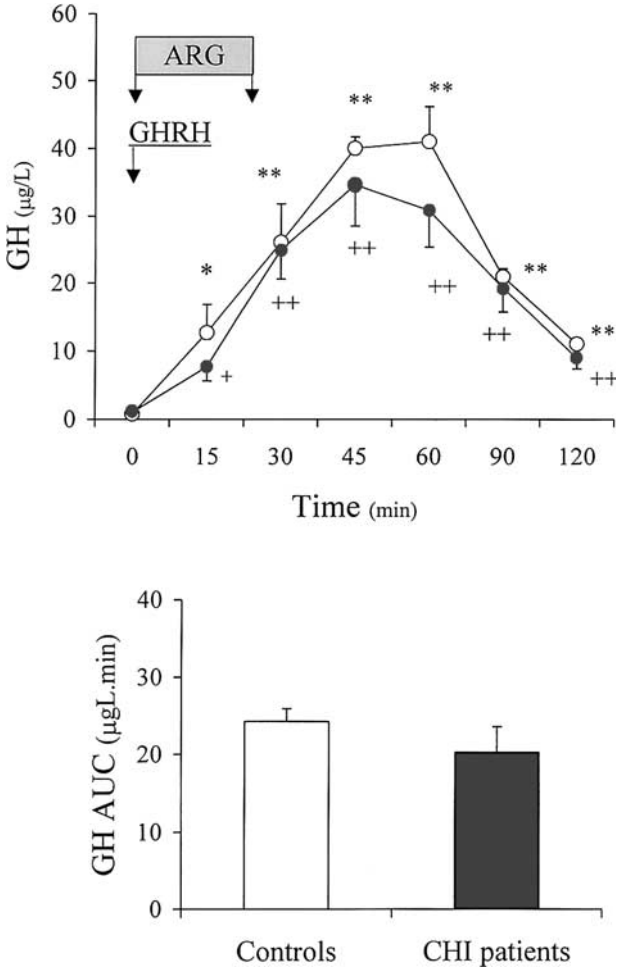

Fig 2. GH response to GHRH plus ARG in severe CHI patients and normal subjects. *$P < .01$, **$P < .001$ *v* basal (normal subjects). $^{+}P < .01$, $^{++}P < .001$ *v* basal (CHI patients).

DISCUSSION

It has been shown that head trauma may be associated with functional alterations in pituitary hormone secretion, which become apparent during the first hours or days after trauma and persist for the duration of the acute illness.[1-3,11,12] However, in these studies, trauma victims underwent pituitary function testing early after injury, and it cannot be excluded that the changes in pituitary hormone profile detected in these patients may have taken part in the acute adaptive response to the injury and/or were related to combinations of pharmacologic therapy used to treat critical illness (glucocorticoids, narcotic analgesics, or dopaminergic agents).[1]

Our study was designed to assess the function of the GH/IGF-1 axis and its neuroendocrine regulation in severe CHI patients during the rehabilitation period when their medical and nutritional status was stable. An understanding of GH status in these patients may help to identify the possible endocrine intervention with adjuvant GH or IGF-1, which could promote an anabolic response and accelerate neuromuscular and cognitive recovery from brain injury during rehabilitation.[20]

The major finding, which emerged from the present study, was the lack of evidence of functional alterations in the GH/IGF-1 axis in a group of injured head trauma patients examined during rehabilitation when nutrition intake had returned to normal.

Basal GH and IGF-1 blood levels were found to be normal in CHI patients and did not significantly differ from those detected in the age-matched control subjects. These data suggest that CHI patients, evaluated at least 1 month after leaving the intensive care unit and on adequate nutritional balance, are not GH-resistant compared with a generation of normal IGF-1 levels. Noteworthy was the demonstration of normal circulating levels of IGFBP-3 and IGFBP-1, which confirmed that our patients were not GH-resistant.[21] The endocrine profile in these patients was the opposite of the state of GH resistance observed in traumatic patients during both the acute or chronic phases of illness when an increase or decrease in GH, respectively, associated with decreased IGF-1 levels, have been shown.[8-12]

Our study showed that GH responses to dynamic challenge tests were not different in CHI patients as compared with controls. The finding of a similar response to GHRH in patients

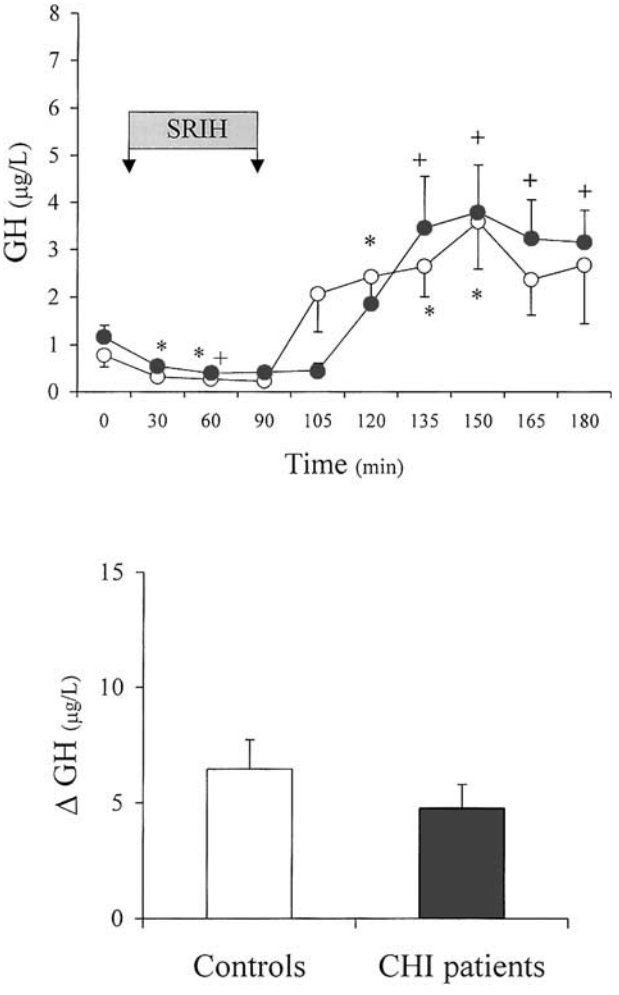

Fig 3. GH response to SRIH withdrawal in severe CHI patients and normal subjects. *$P < .05$ *v* basal (normal subjects), $^{+}P < .05$ *v* basal (CHI patients).

Table 3. Evaluation of GH IGF-1 Axis Function in Severe CHI Patients and Normal Subjects

	Basal GH (μg/L)	GH Peak After GHRH (μg/L)	GH Peak After ARG + GHRH (μg/L)	Δ GH After SRIH (μg/L)	IGF-1 (nmol/L)	IGFBP-3 (mg/L)	IGFBP-1 (μg/L)
Patients							
1	1.46	37.1	70.0	0.6	40.7	3.9	56.6
2	1.41	6.4	82.3	11.9	40.8	2.5	73.0
3	1.35	6.2	68.2	2.1	36.1	5.4	72.1
4	0.73	1.2	14.9	0.3	27.6	4.9	40.0
5	1.05	10.8	14.6	0.6	33.1	4.7	58.0
6	1.82	10.6	42.6	7.4	23.3	4.3	25.5
7	1.07	1.2	15.2	3.8	39.6	2.4	50.2
8	1.08	6.4	38.6	4.8	30.4	4.2	44.1
9	1.56	15.8	30.7	12.8	16.6	2.1	22.2
10	1.28	19.1	46.5	5.3	13.6	3.8	14.0
11	0.67	7.4	30.7	8.6	49.6	3.1	75.0
12	1.19	22.1	37.2	3.8	16.3	2.0	15.0
13	0.32	24.1	17.8	4.3	38.4	4.0	35.0
14	0.90	3.8	25.3	1.0	20.7	3.8	59.2
15	0.22	5.6	8.8	6.2	24.0	3.5	21.3
16	1.96	3.7	24.8	2.9	21.1	2.4	32.4
Controls							
1	0.59	5.0	40.6	14.8	29.5	4.2	38.5
2	1.25	6.2	26.2	4.2	22.6	2.5	31.2
3	0.99	22.4	35.0	6.8	27.2	3.4	41.2
4	0.58	15.8	44.8	10.3	20.6	2.9	29.5
5	0.37	8.0	68.2	1.7	40.7	4.9	61.8
6	1.66	13.1	85.5	8.0	26.0	4.3	35.5
7	0.89	3.5	41.1	0.8	31.9	4.6	31.6
8	1.58	4.3	42.0	3.3	16.8	3.3	22.0
9	1.21	4.6	44.0	7.8	46.9	5.5	70.5
10	0.93	10.1	62.1	7.6	39.2	3.8	56.9
11	1.58	6.3	29.9	1.6	13.3	2.1	16.7
12	1.50	5.4	78.0	10.6	16.9	2.7	51.0

and controls suggests normal pituitary reserve and no abnormalities of GHRH receptors on somatotroph cells. Gottardis et al[22] reported that the GHRH test elicited a significant GH increase in patients who survived after severe head trauma, whereas the GH response was blunted in patients who died. A normal GH response to GHRH has recently been described in injured patients during 2 weeks after head trauma.[2] Nevertheless, although the GH response to GHRH may provide an indication of the pituitary reserve of GH, the GHRH test has not been proven to be reliable in assessing GH secretory status. It is well known that the secretion of GH from somatotropes is regulated by a fine neuroendocrine control system that involves a balanced interplay between the stimulatory GHRH and its inhibitory counterpart, SRIH.[23] Therefore, to evaluate the maximal secretory capacity of somatotroph cells, we measured the GH response to coadministration of GHRH with ARG, which is able to enhance the GHRH-stimulated GH secretion via an inhibition of SRIH tone.[23] Our data show no difference in the GH response to GHRH plus ARG between CHI patients and controls, giving further evidence that the pituitary pool of GH is not impaired. Moreover, the findings suggest that hypothalamus-mediated GH release is normal in these patients, given that ARG is a known inhibitor of hypothalamic SRIH.

Our study clearly shows that SRIH infusion was able to induce a clear-cut increase in plasma GH levels after its withdrawal, and that the magnitude of the rebound GH did not significantly differ between CHI patients and normal subjects. Based on evidence that SRIH withdrawal induces a GHRH-mediated rebound release of GH,[14,15,24] our findings suggest that the activity of GHRH neurons is not impaired in CHI patients after they leave the intensive care unit and are under adequate nutritional balance. From this set of experiments, we conclude that there is no evidence of GH deficiency or significant dysregulation of the GH/IGF-1 axis in CHI patients free of nutritional illness in the rehabilitation phase. On the contrary, a decrease both in the frequency of the GH secretory bursts and in the difference between the number of daytime/nighttime secretory spikes has been reported in severe multiple trauma patients during the immediate postinjury period,[13] indicating that, early after injury, central mechanisms regulating the pulsatility and regularity within the GH secretory pattern may be impaired.

It is noteworthy that in our CHI patients a negative relationship was demonstrated between the magnitude of rebound GH increase after SRIH withdrawal and the levels of CFS, which is a reliable method for assessing cognitive recovery in individuals with brain injury and widely used for measuring outcomes in the inpatient rehabilitation programs.[18,25] Our results suggest a higher activity of GHRH-secreting neurons in patients with a bad recovery of cognitive function. Accordingly, a greater GH response to GHRH and paradoxical GH response to TRH have been reported to be associated with an unfavorable outcome in trauma victims, even if in the acute posttraumatic phase.[2] In

line with these findings, a higher risk of an adverse outcome can be believed to be associated with the presence of accentuated endogenous GHRH tone.

ACTH and cortisol levels remained slightly elevated 1 to 5 months after head trauma in 43.7% and 18.7% of our CHI patients, respectively, suggesting the persistence of functional alterations in hypothalamo-pituitary-adrenal axis. Similarly, abnormalities in cortisol secretory pattern have previously been reported in more than 70% of patients also 2 to 10 months after head trauma.[26] By contrast, other investigators have described no significant changes in ACTH and cortisol levels during the 14 weeks of the posttraumatic period.[27] Moreover, the presence, in some CHI patients, of modestly elevated PRL levels may suggest the presence of alterations in the central neuroendocrine mechanisms involved in the regulation of PRL secretion.

Hypogonadism was detected in 56.2% of our CHI patients. Low T levels are generally found during the acute phase of head trauma and could be related to the catabolic state of critical illness, because they return to normal.[1,6,28] However, serum T concentrations may remain persistently low for 3 to 6 months after the injury, suggesting the presence of permanent hypopituitarism.[29] We cannot exclude that a long-term follow-up of these patients will show the normalization of the pituitary-gonadal axis, as well as the development of other pituitary dysfunctions. In fact, the lag time between head trauma and the diagnosis of hypopituitarism has been shown to vary from a few months to 40 years.[4]

In conclusion, the present study indicates that patients receiving rehabilitation after leaving the intensive care unit for severe traumatic head injury have no significant changes in GH secretion with normal central regulation of the GH/IGF-1 axis and preserved GH responsiveness.

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