A single growth hormone determination 30 minutes after the administration of the GHRH plus GHRP-6 test is sufficient for the diagnosis of somatotrope dysfunction in patients who have suffered traumatic brain injury

A.I. Castro¹, M. Lage¹, R. Peino¹, F. Kelestimir², C. Dieguez³, and F.F. Casanueva¹

¹Department of Medicine, Endocrine Section, Complejo Hospitalario Universitario de Santiago; ²Department of Physiology, Faculty of Medicine, Santiago de Compostela University, Santiago de Compostela, Spain; ³Department of Endocrinology, Erciyes University Medical School, Kayseri, Turkey

ABSTRACT. As hypopituitarism is frequent in patients who have suffered a traumatic brain injury (TBI) a hormonal check-up is necessary. However, the prevalence of TBI is so large that the number of potential candidates to be tested is difficult to manage, in particular for GH deficiency diagnosis that requires cumbersome and expensive dynamic tests. GHRH plus GH-releasing hexapeptide (GHRP-6) is a safe and effective test capable of segregating normal subjects from GH deficient patients. As the GHRH+GHRP-6 test induces GH peaks consistently in the first 30 min, the working hypothesis assessed in this study was whether a single determination of GH 30 min after stimulus could provide the same biochemical classification as the whole secretory curve. A total of 83 subjects who suffered TBI at least one year before the study were administered GHRH 1 µg/kg iv plus GHRP-6 1 µg/kg iv at 0 min, and blood samples were obtained at regular intervals. GH was determined in all samples. An excellent correlation was observed between GH values at 30 min and GH peaks (r=0.972, p<0.0001). When comparing the 30-min GH values against the peaks, the biochemical classification changed only in 5 out of 83 subjects from normal GH secretion to uncertain. Conclusions: The GHRH+GHRP-6 test is convenient, safe and in patients with TBI can be reduced to a single fixed GH determination 30 min after stimulus without losing diagnostic power.


INTRODUCTION

Traumatic brain injury (TBI) was recognized as a cause of neuroendocrine dysfunction in the past century (1-4), a concept reinforced by several case reports showing that severe head traumas induced a variety of pituitary hormone alterations and particularly GH deficiency (5-7). Anecdotic reports of pituitary stalk transection after trauma were published in the sixties and seventies; these were however considered exceptional and in relevant textbooks of endocrinology this etiology was omitted when listing the causes of pituitary dysfunction. Interestingly, in series dealing with hypopituitarism TBI does not appear as a cause but most patients were labelled as idiopathic (8). The situation changed after the year 2000 when some publications showed that TBI-mediated hypopituitarism might be more frequent than had previously been thought (9-11). After such reports, in the last few years several groups have revisited the topic and become interested in the high prevalence of GH deficiency in those patients (12-15), interest enhanced by the fact that the clinical manifestations of a past head injury are very similar to those of GH deficiency in adults (16). In fact, the post-concussion syndrome, very common in patients after TBI, presents with headache, depression, fatigue, irritability, and low working capability, symptoms traditionally associated with severe GH deficiency.

Considering that TBI-mediated hypopituitarism is a very relevant medical problem and that GH deficien-
cy may be partially responsible for the signs, symptoms and poor recovery associated with such brain aggregation, it is now widely accepted that subjects with history of TBI should be tested for GH secretion. However, the potential number of subjects with the inclusion criteria for testing is so high (17) that medical administrations are reluctant to compromise an excessive amount of manpower, money and facilities to such studies, requiring more simple methods in order to undertake epidemiological studies. The combined administration of GHRH plus GH-releasing hexapeptide (GHRP-6) is a potent and reproducible stimulus of GH secretion in man, devoid of side-effects and exhaustively validated on clinical grounds (18-20).

It has been proposed that this combined stimulus may be a suitable test for adults with suspected GH deficiency. It has been reported that in patients with hypopituitarism due to pituitary tumors the procedure of the combined test implicating 5 or 6 GH determinations to identify the peak may be reduced to a single fixed GH determination at 30 min post stimulus without losing the diagnostic capability (21). A shortened test, and therefore a less expensive one, would allow screening for GH deficiency in large populations, something that with other dynamic tests is unaffordable.

In the present work, a group of subjects who had suffered a TBI at least one year before were challenged with the GHRH+GHRP-6 test and the diagnostic accuracy of a fixed single determination of GH at 30 min was evaluated against the GH peak. The aim of the study was to determine whether a single sample 30 min after the test administration would maintain the diagnostic capability of the peak while being equally effective, less expensive and more convenient.

SUBJECTS AND METHODS

Subjects

Subjects with TBI who suffered the injury at least one year before, were recruited from the in-hospital program of the Endocrine Division at the University Hospital, Santiago de Compostela University. All patients were randomly selected from the database of the hospital based on the diagnostic labelling and requiring having been in-patients in the center for at least 24 h before discharge. The exclusion criteria were: a) a serious disability or disease; b) radiotherapy or chemotherapy in the past or corticoid treatment in the last 6 months; c) inability to attend the hospital for evaluation. In total 83 patients were studied, 65 of them men, with a mean age of 44.3±2.0 yr (range 20-81 yr), and body mass index (BMI), kg/m² of 27.2±18.0 (range 17.5-39.1). Body mass composition by impedancemetry and basal complete biochemical and hematological analysis were performed. In addition basal pituitary hormones and peripheral hormones were analyzed and the combined GHRH+GHRP-6 test performed to assess the GH secretory status.

Tests started at 09.00 h after an overnight fast, with the subjects recumbent. An indwelling catheter was placed in a forearm vein and kept permeable with a slow infusion of 150 mmol/l of NaCl. Women were tested in the follicular phase when having regular menstrual cycles. The combined GHRH+GHRP-6 test consisted of an iv bolus injection of 1 µg/kg of GHRH (Geref 1-29 NH2, Geref Serono, Madrid, Spain) immediately followed by an iv bolus injection of 1 µg/kg of GHRP-6 (His-DTrp-Ala-Trp-DPhe-Lys-NH2) obtained from Clinalfa (Lauffelfinger, Switzerland) (20). The first blood sample was obtained at 0 min, and additional blood samples were obtained at appropriate intervals. After centrifugation, plasma samples were stored at -20 C until analysis. Using this test, peaks ≥20 µg/l of GH are considered as normal GH secretion, and peaks ≤10 µg/l are considered as severe GH deficiency. Peaks between those cut-offs are considered “uncertain”, needing further resolution either by performing additional provocative testing or by use of the clinical information (20).

Serum GH concentrations were determined using liquid-phase radioisotopic assay (hGH, Nichols Advantage, San Clemente CA, USA). Hormone levels are presented and analyzed as absolute values (mean±SE) or as a mean GH peak. Differences between groups were tested by Mann-Whitney test. Regression analysis was performed by Pearson’s test. p<0.05 was considered statistically significant.

RESULTS

As a group, the combined administration of GHRH+GHRP-6 induced a rapid and potent GH discharge, that was practically identical in the four samples analyzed after stimulation, i.e. 15, 30, 45 and 60 min (Fig. 1); values at the times 15, 30 and 45 were not significantly different. Interestingly, the mean value at 30 min, 40.0±3.3 µg/l, was nearly identical to the mean of the different peaks obtained, i.e. the so called mean GH peak (44.2±3.5 µg/l).

![Fig. 1 - Mean of GH values obtained at 0, 15, 30, 45 and 60 min after stimulation with the GHRH plus GH-releasing hexapeptide (GHRP-6) test. The mean GH value at 30 min was nearly identical to the mean peak.](image)