Unmasking other pituitary deficits during growth hormone replacement therapy

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1. Introduction

Hypothalamic-pituitary system represents a complex neuroendocrine unit that exerts its influence on the whole organism, by stimulating the target endocrine glands. In turn, the feedback of peripheral hormones strictly controls hypothalamic-pituitary activity. In particular, the growth hormone-insulin-like growth factor I (GH-IGF-I axis) plays an important role in modulating other hypothalamic-pituitary axes.

2. Hypothalamic-pituitary-thyroid axis

There are complex relationships between the GH system and the hypothalamus-pituitary-thyroid (HPT) axis. The reported effects of rhGH administration on thyroid status of patients with growth hormone deficiency (GHD) have been remarkably divergent. Studies on the effects of long-term rhGH replacement treatment in GHD children have described either unchanged [3,21] or decreased serum thyroxine levels [13,15,17,22], along with unchanged [15,21], increased [15,22] and decreased [13,17] serum T3 levels. Transient changes in serum thyroid hormone levels have also been found in GHD children receiving GH [30], whereas no changes have been recorded in a placebo-controlled double-blind trial of GH therapy in non-GHD short children [20]. As far as GHD adults are concerned, one of the few studies on this topic reported no changes in thyroid function after 12 months rhGH therapy. The reasons for the above mentioned discrepancies may be related to either the different methods used for the measurement of thyroid hormones, or the small number of subjects evaluated in the various reports, or the different study protocols (diverse GH doses and timing of the studies). Moreover, most studies have been performed many years ago, when the used pituitary GH preparations were of variable purity and, in some instances, were contaminated with TSH. The introduction of ultrasensitive TSH immunometric assays, the availability of direct methods for the measurement of circulating free T4 and T3, as well as the clinical use of rhGH, have prompted us to study hypothalamus-pituitary-thyroid axis first in a large group of GHD adults and second in a homogeneous cohort of children with either idiopathic isolated GHD or organic multiple pituitary hormone deficiency including GHD. In particular, 66 adults were enrolled in the first study [16], among whom 17 were euthyroid and 49 had central hypothyroidism on adequate L-T4 replacement therapy. GHD was congenital in 31 patients, and was acquired after surgery for organic pituitary lesions in 35 patients. In the second study, 18 children were evaluated, 12 with idiopathic isolated GHD and six with organic multiple pituitary hormone deficiencies. The aim was to investigate the possibility that the administration of low doses of GH could disclose the presence of a mild central hypothyroid state or even to worsen a preexisting central hypothyroidism making it necessary to adjust the L-T4 replacement dose. The most striking result of the first study performed in adults, was that in nearly the 50% of euthyroid patients at baseline, FT4 levels dramatically fell into the hypothyroid range (Fig. 1), thus making it necessary to start L-T4 replacement therapy. Similarly, 9 of 49 central hypothyroid patients (18%) needed an increase in L-T4 replacement dose in order to achieve normal FT4 during rhGH. These results have been confirmed by a recent study involving a large group of patients [1].

As far as the second study is concerned [9], HPT axis was evaluated in children with either idiopathic isolated GHD (IIGHD) or multiple pituitary hormone deficiencies (MPHD) including GHD due to hypothalamic-pituitary organic lesion surgically treated. Evaluating separately these two groups of patients, a significant reduction in FT4 levels was observed on rhGH therapy in both groups. However, no patient with IIGHD became central hypothyroid, while in four of six patients with organic MPHD FT4 fell levels into the hypothyroid range during rhGH (Fig. 2). Notably, two of these patients were euthyroid at the beginning of the study, and their height velocity did not normalize until the achievement of euthyroid-
At the peripheral level, previous studies reported contrasting data on the reduction of cortisol-binding globulin (CBG) induced by rhGH therapy, these discrepancies probably reflecting the use of different rhGH regimens [10,19,27,29]. Moreover, GH may influence the interconversion of hormonally active cortisol and inactive cortisone by modulating the activity of 11β-hydroxysteroid dehydrogenase, particularly the type 1 isoenzyme (11βHSD1) [6,25]. In fact, the activity of 11βHSD1, that acts predominantly as a reductase converting cortisone to cortisol [5,18,24], is inhibited in conditions of GH excess, such as acromegaly, and restored after successful treatment of the disease [14,24]. Conversely, 11βHSD1 activity is enhanced, leading to increased tissue exposure to glucocorticoids in patients with GHD, and reduced by rhGH replacement therapy [5,26–28]. A wide and updated review of the literature on this topic has been recently proposed by Agha and Monson [2].

We have recently evaluated the HPA axis 12 patients (9M-3F; mean age ± SEM: 51 ± 2 years), with adult-onset GHD due to surgically treated pituitary tumors, with preserved HPA function and without evidence of tumor recurrence, before and during rhGH replacement therapy (duration: 31 ± 6 months) [8]. HPA function was assessed by urinary free cortisol (UFC) and morning serum cortisol levels as well as cortisol responses to 1 μg ACTH test (N = 7 patients) or insulin tolerance test (ITT, N = 5 patients) before and during rhGH therapy, the cut-off for the diagnosis of hypoadrenalism being a cortisol peak < 18 μg/dL (< 500 nmol/L) after both stimulatory tests. Serum cortisol and UFC levels were significantly lower on therapy than before while no change in cortisol-binding globulin (CBG) levels was observed. As reported in (Fig. 3), cortisol peak either after ACTH test or ITT was lower on rhGH therapy than before, and cortisol levels at each test time evaluated by two-way ANOVA, as well as cortisol responses measured as AUC value either after 1 μg ACTH or after ITT were significant lower on rhGH (P < 0.005) in comparison with pre-treatment values. According to the diagnostic criteria, central hypoadrenalism was detected in 9 of 11 patients.

In conclusion, low GH and IGF-I levels, likely enhancing the conversion of cortisone to cortisol, may mask a condition of central hypoadrenalism. Therefore, the reassessment of HPA function in patients with organic GHD during rhGH therapy is mandatory.

To confirm this hypothesis, we have further evaluated the HPA axis in ten children (5M and 5F, mean age 12.2 ± 1.0 years, mean height SDS −1.9 ± 0.8) with idiopathic isolated GHD and normal pituitary MRI. HPA function was assessed at baseline and on rhGH (mean duration: 10.9 ± 2.9 months; mean dose: 0.030±0.002 mg/kg bw per day) by serum cortisol levels before and after appropriate provocative stimuli: 1 μg ACTH test (N = 5 patients) or insulin tolerance test (ITT, N = 5 patients). All children were evaluated with the same stimulation test either before or on rhGH therapy. Central hypoadrenalism was excluded by the presence of either a peak > 500 nmol/l or a rise in cortisol levels > 200 nmol/l, after both tests. Plasma ACTH and serum IGF-I levels were also determined. During rhGH, serum IGF-I

### 3. Hypothalamic-pituitary-adrenal axis

Complex and often contradictory relationships between the GH-IGF-I system and the hypothalamus-pituitary-adrenal axis (HPA) both at central and peripheral levels have been reported [7,10,12,19,23,27,29]. In particular, although ACTH is the primary regulator of adrenal cortex growth and function, the GH-IGF-I system seems to exert a positive effect on cortisol biosynthesis, probably by inducing the expression of steroidogenic acute regulatory protein (StAR) [12]. In contrast to this positive effect, it has been suggested that the acute increase of IGF-I may cause, via a negative feedback mechanism, a reduction of both GH and cortisol in animals [23]. However, these data have not been confirmed by a recent study reporting the effect of recombinant human IGF-I on HPA axis in healthy subjects [7].

![Fig. 1. Serum FT4 levels before (circle) and after (triangle) 6-month rhGH therapy in 17 euthyroid patients (ten at low and seven at high rhGH regimen, panels A and B, respectively). The dotted line indicates the lower limit of the normal FT4 range.](image1)

![Fig. 2. Serum FT4 levels before (square) and after (triangle) rhGH therapy in children with idiopathic isolated GHD (IIGHD) and with multiple pituitary hormone deficiency (MPHD).](image2)
levels normalized and mean serum cortisol levels, though showing a slight decrease, did not significantly differ from those recorded at baseline (212 ± 25 vs. 258 ± 45 nmol/l, respectively, \( P = \text{NS} \)). The mean serum cortisol peak after both provocative tests was the same on rhGH therapy and at baseline and plasma ACTH levels did not vary significantly. In conclusion, no child with IIGHD developed central hypoadrenalism on rhGH, contrary to what observed in patients with organic GHD, further supporting the view that only in patients with organic multiple pituitary hormone deficiencies, GH deficiency masks the presence of a hidden central hypoadrenalism, as previously observed for central hypothyroidism.

4. Hypothalamic-pituitary-gonadal axis

Little is known about the effect of GHD and rhGH replacement on the hypothalamus-pituitary-gonadal axis (HPG). The few studies performed on this topic reported contrasting data. In a double-blind placebo controlled trial performed in young males with childhood-onset GHD, Juul et al. [11] concluded that rhGH administration does not influence the HPG axis. Conversely, another study [4] carried out on males with idiopathic isolated GHD, showed that rhGH treatment displays an evident effect upon Leydig cell function, increasing testosterone response to chorionic gonadotropin (CG). However, these studies included patients with either idiopathic or organic GHD or different HPG axis statuses, being either normogonadic or hypogonadic under treatment with testosterone. Moreover, rhGH doses employed in these studies were 2- to 3-fold higher than those presently used, making difficult to distinguish physiological from pharmacological rhGH effects.

Quite recently, we investigated the hypothalamic-pituitary-gonadal axis (HPG) in 12 adult males (mean age 47±8 years) with organic GHD and normal HPG axis. Serum levels of testosterone, LH and FSH (basal and after GnRH stimulation test), SHBG and IGF-I and percent of body fat (BF%) were evaluated before and during rhGH (mean dose 0.24 ± 0.02 mg/day for 13 ± 1 months). Serum IGF-I levels normalized during rhGH and BF% significantly decreased. Serum testosterone levels significantly decreased (from 18.1 ± 1.7 to 14.2 ± 1.6 nmol/l, \( P = 0.01 \)), along with a parallel and significant decrease of serum SHBG (from 31.1 ± 3.6 to 24.3 ± 2.3 nmol/l, \( P < 0.05 \)). Thus, calculated free testosterone (cFT, calculated from values of testosterone, SHBG and albumin - for the default albumin concentration of 4.3 g/Dl — by using mass — action equations) did not change. Remarkably, 2 of 12 patients showed total testosterone levels below the normal range on rhGH without change in cFT and signs or symptoms of hypogonadism. Finally, no difference was found in basal and GnRH stimulated gonadotropins levels. In conclusion, the condition of GHD does not seem to be a bias in the diagnosis of central hypogonadism, at variance with what observed for central hypothyroidism and hypoadrenalism. However, the significant decrease in serum testosterone levels, strictly related to SHBG decrease, suggests that evaluation of HPG axis during rhGH cannot be based on the measurement of total testosterone levels, but should mainly rely on calculation of cFT and on a careful clinical evaluation, in order to avoid unnecessary replacement therapy.

5. Conclusion

In conclusion, patient with GHD is a complex patient, in which GHD may be due to organic lesion of hypothalamic-pituitary region and be associated with MPHD. The state of untreated GHD may mask in a consistent number of cases a central hypothyroid and/or hypoadrenal condition, whose diagnosis becomes possible only after rhGH replacement. Therefore, a reassessment of thyroid and adrenal function through hormonal measurements and appropriate testing is mandatory during rhGH therapy in patients with organic GHD.

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References


