

EFFECTS OF GROWTH HORMONE REPLACEMENT THERAPY ON THYROID FUNCTION TESTS IN GROWTH HORMONE DEFICIENT CHILDREN

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Abstract- There are numerous, often contradictory reports on the effect of growth hormone (GH) therapy on thyroid function. These reports prompted us to evaluate the impact of GH therapy on thyroid function in previously euthyroid children with GH deficiency. Twenty five clinically and biochemically euthyroid children with GH deficiency were studied. A thyroid profile (T4, Free T4, T3 and TSH) was performed at baseline and 3, 6 and 12 months after GH therapy in 21 children with idiopathic growth hormone deficiency (group A) and 4 children with organic GH deficiency (group B). We observed a significant reduction in serum T4 and free T4 concentrations during GH therapy in both groups ($P < 0.01$). No patient in group A had free T4 levels fell into the hypothyroid range, while in one of four patients in group B, free T4 value fell into the hypothyroid range during GH therapy. In both groups, no significant variation in serum TSH and T3 was recorded at any time. Our data suggest that GH therapy can introduce changes in thyroid function and so confirm the need of a careful monitoring of thyroid function in particular in children with organic GH deficiency during long-term GH therapy.

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INTRODUCTION

Growth hormone (GH) regulate several other hormonal systems and vice versa. There are complex relationships between GH system and hypothalamic-pituitary-thyroid axis and the effects of GH replacement therapy on thyroid function still remain controversial (1, 2).

We know that GH enhances the extrathyroidal conversion of T4 to T3 and decreases conversion of T4 to reverse T3 (rT3) (2-8). Most studies have reported significant changes in thyroid function,

including a slight decline in serum T4, rT3 and TSH levels and an elevation in T3 levels caused by an increase in peripheral conversion of T4 to T3 and decrease conversion of T4 to rT3, selectively mediated by GH (4, 5, 9, 10).

The development of central hypothyroidism has been reported during GH therapy in children initially thought to have normal thyroid function. The actual incidence, however, is controversial, with some studies showing a rare (11-16) and others a high (17-21) occurrence. A recent analysis in over 2300 patients showed that 29% of children with idiopathic GH deficiency and 61% of children with organic GH deficiency were also receiving thyroid hormone therapy during treatment with recombinant human GH therapy (11).

These contradictory results motivated us to investigate changes in thyroid hormone levels with GH therapy and to determine the necessity of thyroid

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hormone assessment in these patients. To our knowledge, no study focusing on the occurrence of central hypothyroidism in previously euthyroid children during GH therapy have been conducted in Iran.

MATERIALS AND METHODS

Twenty five euthyroid children (13 girls and 12 boys; mean age 8.7 ± 3.1 years) with GH deficiency who consecutively attended the Pediatric Endocrine Clinic of Imam Khomeini Hospital affiliated to Tehran University of Medical Sciences from January 2005 to February 2006 were studied and followed for 12 months. This study was approved by the Human Research Ethics Board of Tehran University of Medical Sciences and we obtained informed consent from parents of all participants.

GH deficiency was defined as a peak GH level less than 10 ng/mL in response to two standard stimulation tests (Levodopa + Inderal followed by oral clonidine) in a patient with a growth velocity of 5 cm/yr or less if younger than 5 yr or of 4 cm/yr or less if older than 5 yr.

All patients were prepubertal, were taking no thyroid supplementation. None of the patients showed multiple pituitary hormone deficiency. No patient was taking any medication known to interfere with thyroid metabolism. Twenty-one patients had idiopathic GH deficiency (group A) and four patients (group B) had organic GH deficiency (two had empty sella syndrome and two had operated for craniopharyngioma). All patients were initially euthyroid. Concentrations of thyroid hormone levels were determined in sera at baseline and 3, 6, and 12 months after GH therapy began. Free T4, T4 and T3 were measured by radioimmunoassay (RIA) and TSH was measured by immunoradiometric assay (IRMA).

SPSS 10/0 software (SPSS, Chicago III) was used for statistical analysis. Comparisons between the sampling points for thyroid values were made by analysis of variance (ANOVA) and paired *t* test ($P < 0.05$ was considered significant).

RESULTS

There were no physical signs of hypothyroidism in these patients examined during 12 months of GH

administration.

In both group, a significant reduction in T4 levels ($P < 0.01$) occurred during GH therapy. A similar trend was observed for FT4 values. No patient in group A had FT4 value in the hypothyroid range and the satisfactory growth rate was achieved. In group B, in 1 of 4 patients, FT4 level fell to hypothyroid range and did not returned to the values prior to the treatment; the patient's height velocity did not normalize until the achievement of euthyroidism through appropriate thyroxine substitution.

No significant variation in serum T3 and TSH was recorded in either group along the study.

DISCUSSION

In present study, the alteration in thyroid hormone function during the first year of GH therapy in GH deficient children who were initially euthyroid was documented only by the decline in serum T4 and FT4 levels and all T3 and TSH levels had no significant changes along all the study period. Although almost all children showed a decline in T4 and FT4 values, only in one patient with organic GH deficiency T4 and FT4 values was below the normal range.

Our findings are in accordance with those reported by Seminara and collaborators in 19 GH deficient children (22), by Portes and Co-workers in 20 clinically and biochemically euthyroid GH deficient children (23) and by Giavolli and colleagues (24). In the latter study, the authors studied 20 euthyroid children with isolated idiopathic GH deficiency and 6 children with GH deficiency due to organic lesions. They concluded that contrary to that observed in patients with organic GH deficiency, GH replacement therapy does not induce central hypothyroidism in children with idiopathic GH deficiency. The study by Agha *et al.* in 243 patient with severe GH deficiency due to various hypothalamic-pituitary disorders, demonstrates that administration of recombinant human GH (rhGH) to adults with severe GH deficiency leads to clinically relevant central hypothyroidism, which manifest as a decline in serum concentration of T4 or FT4 values (25). These results further supporting the view that

GH deficiency masks a state of central hypothyroidism in a significant portion of hypopituitary patients that become manifest only during GH therapy.

Many contrasting data have been reported about the effect of GH therapy on thyroid function. In contrast with our findings, Wyatt and collaborators (26) and Vieira and co-workers (27) did not find any significant reduction in total T4 and FT4 values at the end of 12 months of GH administration.

Some investigators have suggested that GH inhibits TSH release, perhaps via increased somatostatergic tone or by the negative feedback of an increased T3 values (3, 7, 8, 28). Others, like us, have found no significant change in TSH levels in GH deficient children during GH therapy (14, 29, 30). However, the effects of GH therapy on thyroid function among previous reports have shown remarkable discrepancies, probably due to differences in hormone assay methods, diagnostic criteria, patient selection, GH dose, duration of treatment and study design.

In summary, the current study was in line with many previous reports placing patients with GH deficiency in particular organic GH deficiency at an increased risk for developing central hypothyroidism during GH replacement therapy and so careful monitoring of thyroid function, particularly by means of the direct measurement of circulating FT4 is mandatory.

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Conflict of interests

The authors declare that they have no competing interests.

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