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ORIGINAL ARTICLE

Effect of growth hormone therapy on Taiwanese children with growth hormone deficiency

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KEYWORDS
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Background/Purpose: Human growth hormone (GH) has been successfully used in children with GH deficiency (GHD). However, there are few published data on the effect of GH in Taiwanese children with GHD.

Methods: We performed a retrospective cohort study to identify factors influencing the effect of GH therapy on ethnic Chinese children with GHD in Taiwan. Idiopathic GHD can be classified into isolated GHD (IGHD) and multiple pituitary hormone deficiency (MPHD). The study looked at the effect of GH on the auxological, biochemical, and imaging parameters of 51 patients (13 girls and 38 boys) in three different diagnostic groups: MPHD ($n = 12$), IGHD ($n = 8$), and transient GHD (TGHD; $n = 31$). TGHD is defined as a GH peak >10 μg/L in re-evaluation by two GH stimulation tests approximately 6 months after discontinuation of GH therapy.

Results: The height velocity for first-year GH therapy was 7.61 ± 1.46, 8.14 ± 1.92, and 9.99 ± 2.75 cm/y in the TGHD, IGHD, and MPHD groups, respectively. After post hoc comparison, the MPHD group had a significantly accelerated height velocity in the first year compared to the TGHD group. Correlation analysis showed that a change in height standard deviation score (SDS) in the first year had a significant negative correlation with the following variables: peak GH ($r = -0.52$, $p < 0.001$), pretreatment height SDS ($r = -0.49$, $p < 0.001$), and height-target height (Ht-TH) SDS ($r = -0.49$, $p < 0.001$). Change in height SDS in the first 2 years had a significantly negative correlation with peak GH ($r = -0.51$, $p < 0.001$), insulin-like growth factor-1 SDS ($r = -0.35$, $p = 0.022$), height SDS ($r = -0.60$, $p < 0.001$), difference between bone age and chronological age ($r = -0.46$, $p = 0.001$), and Ht-TH SDS ($r = -0.50$, $p = 0.001$). After using multiple linear regression, the pretreatment GH peak value was found to be significantly associated with height increments after 1 year of GH treatment ($B = -0.07$, $p = 0.014$).

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Conclusion: The administration of GH to children with GHD results in a pronounced acceleration in linear growth during the first year of treatment, especially in those with MPHD. The diagnosis of GHD requires comprehensive auxological, biochemical, and brain magnetic resonance imaging assessment. We also suggest that patients with GHD, specifically IGHD, must undergo a re-evaluation of GH secretion after completion of GH therapy.

Introduction

For more than 50 years, human growth hormone (GH) has been used in GH deficiency (GHD).There are few published data reporting factors predicting the effect of GH on Taiwanese children with GHD. The conventional study of GH secretion, diagnosis, and treatment of GHD during childhood and adolescence is still controversial. The diagnosis of GHD is a multifaceted process requiring comprehensive clinical and auxological assessment, combined with the biochemical testing of the GH—insulin-like growth factor (IGF) axis and evaluation with brain magnetic resonance imaging (MRI).[1]

The etiology of GHD may be idiopathic or associated with organic causes, such as tumor, surgery, or irradiation of the sellar area. Idiopathic GHD may be classified into isolated GHD (IGHD) and multiple pituitary hormone deficiency (MPHD) by its association with a deficiency of one or more anterior pituitary hormones during provocation tests. Morphological alterations on brain MRI in patients with GHD include pituitary hypoplasia, absence or interruption of the pituitary stalk, and an absent or ectopic posterior lobe.

Most subjects previously labeled as having IGHD with a normal pituitary MRI or an isolated small pituitary gland have been reported to show a normalization of GH secretion after completing their growth.[2–4] This represents a condition of transient GHD (TGHD) of unknown origin, an absence of pubertal steroids, or simply unreliability and variability of the GH provocation tests.[5]

In 2004, we reported that MRI findings in the hypothalamic-pituitary area can be correlated with the severity of hypopituitarism.[6] Patients with MPHD had a low height, peak GH level, and IGF-1 standard deviation score (SDS) and greater bone age (BA) delay than partial those with IGHD or severe IGHD before GH therapy. In this investigation, we performed a retrospective cohort study of the effect of GH on the auxological, biochemical, and imaging parameters of 51 ethnic Chinese children in three different diagnostic groups of GHD (TGHD, IGHD, and MPHD) and analyzed the variables predicting the response to GH treatment.

Patients and methods

Patients

The retrospective cohort study comprised 51 patients (13 females and 38 males) with GHD who were receiving GH treatment and were followed up in the Division of Pediatric Endocrinology and Genetics at Linkou Chang-Gung Memorial Hospital from Aug 1996 to July 2010. Patients presenting the following criteria were diagnosed as having GHD: (1) peak GH response less than 10 μg/L after two GH provocation tests (insulin and clonidine stimulation test); (2) severe short stature (height $< 3^{rd}$ centile) or low height velocity < 4 cm/y[7]; and (3) BA[8] retarded by at least 2 SDS from the chronological age (CA). The height of the patient is expressed as an SDS (see the supplementary methods), and the report of the Department of Physical Education and Sports of the Ministry of Education in Taiwan was used as to define the standards.[9]

Anterior pituitary function was evaluated by combined pituitary function testing: insulin tolerance test for GH and cortisol secretion; thyrotropin-releasing hormone test for thyroid-stimulating hormone (TSH) and prolactin secretion; and gonadotropin-releasing hormone test for follicle-stimulating hormone and luteinizing hormone secretion (see the supplementary methods).[10] None of the patients received sex steroid priming before the GH stimulation tests.

Methods

Based on the results of endocrinological evaluation, patients were divided into three groups: (1) patients with MPHD ($n = 12$), defined as GH peak concentration < 10 μg/L accompanied by a deficit of one or more anterior pituitary hormones; (2) patients with IGHD ($n = 8$), defined as a GH peak < 10 μg/L; and (3) patients with TGHD ($n = 31$), defined as a GH peak >10 μg/L on re-evaluating GH status by pharmacological stimulation (insulin stimulation test or clonidine test) approximately 6 months after discontinuation of GH therapy considering the initial diagnosis as MPHD ($n = 2$) or IGHD ($n = 29$) (Fig. 1).

MRI was performed after diagnosis of GHD for 50 patients (see the supplementary methods). The one remaining patient underwent a brain computed tomography study. All images were evaluated by one radiologist. The height of the pituitary gland was measured on the midline sagittal plane perpendicular to the floor of the sella turcica to the highest point of the surface of the superior gland, located at the point of insertion on the pituitary stalk.[11] The presence of the stalk was determined, and its width was evaluated on both the coronal and sagittal images. The stalk was classified as normal or as showing dysgenesis [including being thin (<2.13 mm),[12] interrupted,[13] or absent]. The bright spot of the posterior pituitary was evaluated in both the coronal and sagittal images. It was considered to be ectopic if located outside the sella turcica.[13] The age of the 50 patients at the time of MRI ranged from 3.21 to 19.12 years (10.69 ± 3.24 years).

In the MPHD group, two patients had GHD accompanied by TSH, adrenocorticotropic hormone, and gonadotropin deficiency, two had GHD with TSH and gonadotropin deficiency, three with TSH deficiency alone, two with