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Comparison between weight-based and IGF-I-based growth hormone (GH) dosing in the treatment of children with GH deficiency and influence of exon 3 deleted GH receptor variant

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Abstract

Objective: Compare the most frequently used weight-based GH dosing with an IGF-I level-based strategy in the treatment of children with severe GH deficiency. Additionally, analyse the influence of the GH receptor exon 3 polymorphism on IGF-I levels during GH therapy.
Design: Thirty children with GH deficiency on treatment with GH for 4.3 ± 3.2 yr in a single University Hospital were divided in group W (weight-based GH dosing) and group I (IGF-I-based dosing). In group I, GH doses were changed by 8.3 μg/kg d to maintain IGF-I levels between 0 and +2 SDS, whereas in group W the dose was fixed at 30 μg/kg d in prepubertal and 50 μg/kg d in pubertal patients. Growth velocity was measured after 1 yr, IGF-I and IGFBP3 levels quarterly. GH receptor exon 3 was genotyped by PCR.
Results: Most patients in Group I reached target IGF-I levels after 6 months with a GH dose ranging between 25 and 66 μg/kg d (mean ± SD, 38 ± 8). Each change of 8.3 μg/kg d of GH dose, resulted in change of 1.17 ± 0.6 SDS of IGF-I levels. Mean IGF-I levels were higher in Group I 0.8 ± 0.5 SDS than in Group W -0.3 ± 1.9 SDS ($p < 0.05$), but growth velocities were similar, 6.8 ± 2.6 cm/yr and 6.9 ± 2.6 cm/yr ($p =$ NS), respectively. Serum IGFBP3 levels were similar in both groups and were less useful to individualize GH therapy. Even treated with a similar mean GH dose, patients carrying at least one GH receptor d3-allele reached higher IGF-I levels (0.7 ± 1.2 SDS) than those homozygous for the full-length allele (-0.3 ± 1.2 SDS; $p < 0.05$), however, growth velocities were not different.
Conclusions: By adjusting the GH dose, it was feasible to maintain IGF-I in the desired range (0–+2 SDS). Patients carrying at least one GH receptor d3-allele reached higher circulating IGF-I levels than those homozygous for the full-length allele. A multiple regression analysis failed to demonstrate an independent influence of IGF-I levels on GV during the 12 months of observation.

Keywords: Dwarfism, pituitary; Growth hormone deficiency; Growth hormone therapy; IGF-I levels; Growth hormone receptor, exon 3 variant

1. Introduction

There is no consensus regarding the optimal dosing of recombinant growth hormone (rGH) for children with growth hormone deficiency (GHD). Currently, most pediatric endocrinologists use a fixed rGH dose

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calculated according to weight or body surface area. Some children with GHD do not achieve normal height, and some, even reaching normal height, do not achieve the genetic target height determined by their parents' heights [1]. In addition to rGH dose, other variables such as late diagnosis and treatment, lack of compliance and nutritional inadequacy can influence the growth response. At the same time, some children with GHD develop acromegalic characteristics after long-term treatment with rGH [2–4]. The existence of a specific and effective marker to individualize rGH dose would be useful to control therapy of children with GHD. This marker ideally should be obtained in a shorter time interval than growth velocity (GV), which requires several months of follow-up.

IGF-I is responsible for most anabolic and mitogenic GH actions and consequently for growth promotion and development of organs and tissues during all growth stages [5]. IGFBP3 is the main of several proteins which increases IGF-I half-life, transports it to the target cells and guides its interaction with membrane receptors.

Serum IGF-I and IGFBP3 concentrations are usually reduced in patients with GHD. Presently, their main clinical use is limited to contributing to the diagnosis of GHD, to control safety and to ensure adherence to rGH therapy. Recently, an IGF-I based dosing of rGH therapy in children was reported [6].

Epidemiological studies on breast [7], prostate [8] and colon [9] cancers have indicated that IGF-I concentrations at the superior quartile of the normal range are associated with augmented risk for these neoplasias. Furthermore, the combination of higher IGF-I concentrations and lower IGFBP3 concentrations have yet been associated with a major risk profile for prostate [10] and breast cancer [11] whereas lower IGF-I concentrations with higher IGFBP3 concentrations is associated with a more favourable risk profile [12]. Therefore, it is advisable to evaluate the IGF-I/IGFBP3 ratio during long-term rGH therapy.

Several studies showed the different variables that could influence the response to rGH therapy in children with GHD [1,13–16]. These factors explain only partially the interindividual variability of response; implicating that other factors must be involved. Genetic factors begin to be explored and the GH receptor (GHR) gene is an obvious candidate. Two of the more common GHR isoforms in humans are generated by retention (full-length GHR–GHRfl) and by exclusion of exon 3 (exon 3 deleted GHR–GHRd3) [17]. Dos Santos et al. reported that patients born small for gestational age or with idiopathic short stature with at least one GHRd3 allele had a 1.7–2 times greater growth acceleration after 2 yr treatment with rGH than patients homozygous for GHRfl [18]. The influence of this polymorphism on the response to rGH treatment in patients with GH deficiency has been controversial: the GHRd3 genotype was associated to a better growth response during the first year of treatment and to a higher final height [19] in patients with very low GH levels but not in two studies with less stringent diagnostic criteria [20,21]. Children with GHD with at least one GHRd3 allele had a tendency toward higher IGF-I concentrations during rGH therapy [20].

The aim of the present study was to compare growth velocities and IGF-I levels of children with GHD treated with a fixed weight-based with those treated with individualized rGH dose adjusted by IGF-I levels measured during treatment. We also compared the circulating IGF-I levels in response to the different rGH doses with the *GHR* exon 3 genotype of these patients.

2. Patients and methods

2.1. Subjects

Informed parental consent, patient assent, and approval by the Hospital Ethics Committee were obtained before initiating the studies. Thirty children (18 boys) with GHD from a single centre who were already on treatment with rGH for 4.3 ± 3.2 yr were studied. Inclusion criteria were: isolated GHD or combined pituitary hormone deficiency, chronological age <17 yr, bone age $\leqslant 13$ yr in girls and $\leqslant 14$ yr in boys. Exclusion criteria were: hepatic disease, uncontrolled diabetes mellitus or hypothyroidism, anorexia, malnutrition, severe obesity, other chronic disease, lack of adherence to rGH treatment (more than 2 cumulative months without GH use) or irregular replacement for other hormonal deficiencies. Magnetic resonance imaging (MRI) of the hypothalamic-pituitary region was performed in all patients in a 1.5 Tesla unit (Signa, GE, Milwaukee, WI) [22]. Patients with central nervous system tumours, meningoencephalocele, and previous radiation therapy were also excluded.

Diagnosis of GHD had been established by short stature (height < 2 SDS for age and sex), exclusion of other causes of short stature, and failure to achieve GH levels higher than 3.3 ng/ml by immunofluorometric assay (IFMA) or 7.0 ng/ml by immunoradiometric assay (IRMA) after stimulation by both clonidine and insulin-induced hypoglycaemia tests, on separate occasions [23]. According to the hormonal response to the combined test (insulin + TRH + GnRH), patients were classified as isolated GHD (IGHD) or combined pituitary hormone deficiency (CPHD) [22,24].

The patients with GHD were invited to participate in the study and were sequentially distributed into one of the two groups, Group I (IGF-I-based dose) or Group W (weight-based dose), in a manner as to obtain in each group an equal distribution of the following parameters that were considered important: age, sex, IGHD or