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Corneal thickness in children with growth hormone deficiency: The effect of GH treatment

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ABSTRACT

Objective: The eye represents a target site for GH action, although few data are available in patients with GH deficiency (GHD). Our aim was to evaluate central corneal thickness (CCT) and intraocular pressure (IOP) values in GHD children to assess the role played by GHD or GH treatment on these parameters.
Design: In 74 prepubertal GHD children (51 M, 23 F, aged 10.4 ± 2.4 years) we measured CCT and IOP before and after 12 months of treatment. A baseline evaluation was also made in 50 healthy children matched for age, gender and body mass index. The study outcome considered CCT and IOP during treatment and their correlations with biochemical and auxological data.
Results: No difference in CCT and IOP between GHD children at baseline and controls was found (all $p > 0.005$). GHD children after 12 months of therapy showed greater CCT (564.7 ± 13.1 μm) than both baseline values (535.7 ± 17 μm; $p < 0.001$) and control subjects (536.2 ± 12.5 μm; $p < 0.001$), with a concomitantly higher corrected mean IOP (15.6 ± 0.7 mm Hg; $p < 0.001$) than both baseline (12.5 ± 0.8 mm Hg; $p < 0.001$) and controls (12.3 ± 0.5 mm Hg; $p < 0.001$), without correlation with auxological and biochemical parameters.
Conclusions: 12 months of GH treatment in children with GHD, regardless of auxological and biochemical data, affect CCT and IOP. Our findings suggest careful ocular evaluation in these patients to prevent undesirable side effects during the follow-up.

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1. Introduction

Although the intrinsic mechanism of growth hormone (GH) actions on eyes is still not fully known, it is well established that the eye represents a target site for GH action. GH may have endocrine, autocrine or paracrine roles in ocular development and growth [1]. In this connection, GH is present in the human retina and vitreous fluids [2] and Harvey et al. identified GH immunoreactivity in the retina of chicks, mice and rats, suggesting a role for GH in neurogenesis or ocular development [3–5]. The role of GH in retinal function is supported by the evidence of optic nerve and disc dysfunction in patients affected by GH deficiency (GHD) [6,7]. Many years ago it was suggested that GH might facilitate a condition of glaucoma, demonstrated by higher GH levels after intravenous arginine administration in patients with open-angle glaucoma than in control subjects, supporting the hypothesis that increased plasma GH levels may interfere with regulation of ocular pressure [8]. In addition, the importance of GH action in ocular development is demonstrated by the ocular abnormalities that can occur in patients with pituitary GH excess or deficiency [7,9–12]. Elevated intraocular levels of insulin growth factor-I (IGF-I) in acromegalic patients have previously been reported [11] while in patients with primary GH insensitivity treated with IGF-I therapy, a greater average ocular dimension, including the average corneal curvature, than that observed in untreated patients has been demonstrated, further supporting the effect of IGF-I on ocular growth [13]. The only study that performed a complete ocular evaluation, including the measurement of central corneal thickness (CCT) and intraocular pressure (IOP), in children affected by GHD already under GH-treatment, concluded that an increased CCT, probably associated with a shorter axial length, can represent a sign of a delayed growth of the eye in these patients [14]. In addition, more recently Youngster et al. showed increased IOP in GH-treated children [15]. However, to the best of our knowledge, CCT and IOP have never been prospectively assessed in GHD patients, i.e. before and after GH treatment. The aim of this study was to evaluate CCT and IOP values in children with isolated idiopathic GHD at before and after 12 months of GH therapy.

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2. Materials and methods

2.1. Patients

For the purpose of this study, 74 consecutive children (51 males and 23 females, mean age 10.4 ± 2.4 years) affected by newly diagnosed isolated idiopathic GHD coming to the Units of Endocrinology of the University of Palermo from Jan 1st 2010 to December 31st 2012 were prospectively enrolled. Fifty healthy children, matched for age (mean age 11 ± 2.6 years), gender and body mass index (BMI), were recruited as controls among the siblings of the patients and the children of medical and paramedical personnel of the Department and their relatives.

All children evaluated were in the 1st stage of sexual development according to the criteria of Marshall and Tanner [16]. The diagnosis of GHD was established by the clinical, auxological and biochemical criteria of the GH Research Society [17]. All patients underwent IGF-I assessment, an insulin tolerance test (ITT) and a GHRH plus arginine (GHRH-Arg) test. GHD was demonstrated by the failure of GH to respond to the two stimuli, with GH peaks below 10 and 20 μg/l, respectively. The subjects with a diagnosis of GHD received GH once daily at bedtime with a pen injection system. The initial daily dose was 0.025 mg/kg. During the study, the GH dose administered was adjusted in order to maintain serum IGF-I levels within the normal range for age, with a maximum dose of 0.035 mg/kg. Children with a therapy follow-up of less than 12 months were excluded from this analysis. Similarly, children with already known ocular clinically relevant disease, severe refractive errors, or family history of ocular hypertension or glaucoma were excluded from the analysis.

2.2. Study design

This was an analytical, prospective study to analyze CCT and IOP and their relationship with biochemical and auxological data in GHD children. In all subjects, according to our fixed internal protocol, we measured body height (standard deviation, SD), body mass index (BMI) and bone age. We calculated the ratio between the bone age and the chronological age (normal = 1) and we showed the data as a bone/chronological age ratio. All subjects underwent ophthalmological evaluation, including measurement of CCT and IOP by applanation tonometry. GHD children were evaluated at baseline and after 12 months of GH treatment, while controls were evaluated once at baseline. The study outcome considered CCT and IOP during treatment and their correlations with biochemical and auxological data. The Institutional Ethics Committee of the University of Palermo approved this study. At the time of first observation, an informed consent for the scientific use of the data was obtained from parents. This research has followed the Tenets of the Declaration of Helsinki.

2.3. Ocular evaluation

CCT was measured by very high-frequency ultrasonic contact pachimetry (Pachpen Accutome 24-5100) after local anesthetic instillation, with a sound velocity of 1640 m/s and a mean accuracy of ±5 μm. The value of CCT was performed taking the average of five consecutive pachimetry measurements.

IOP was measured by means of Goldmann applanation tonometry. A single ophthalmologist performed both examinations in all children.

We showed the CCT and IOP values as the average from both eyes.

2.4. Hormone and biochemical assays

During the entire study period, in our centralized laboratory the GH levels were assayed by immunoradiometric assays (Radim, Pomezia, Italy), with an assay sensitivity of 0.05 μg/l. The intra-assay coefficients of variation (CV) were 2.5–3.9% and the inter-assay CV were 3.8–5.0%. Serum total IGF-I was assayed in the same laboratory with the ELISA method (OCTEIA IGF-I kit, IDS Inc., Fountain Hills, AZ, USA). The sensitivity of the method was 1.9 μg/l. The inter- and intra-assay CV values were 7–7.1 and 2.3–3.5% respectively, at IGF-I levels of 90.7–186 and 66.7–120.9 μg/l respectively. The normal ranges (males and females combined) of total IGF-I levels (μg/l) were the following: 12–108 (0–1 years); 13–100 (1–3 years); 26–280 (3–6 years); 85–230 (6–9 years); 98–404 (9–12 years); 142–525 (12–15 years); and 146–415 (15–20 years).

2.5. Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± standard deviation (SD) for continuous variables; rates and proportions were calculated for categorical data. Normality of distribution for quantitative variables was assessed with the Kolmogorov–Smirnov test. Differences between continuous variables were analyzed using the Mann–Whitney *U*-test, while differences between categorical variables were analyzed by using the χ^2-test and Fisher's exact test, when appropriate. Differences between paired continuous variables in the GHD group (before and after 12 months of therapy) were analyzed using the Wilcoxon test. Correlations among continuous variables without normal distribution were determined using Spearman's test (non-parametric equivalent for Pearson test). A p value <0.05 was considered statistically significant.

3. Results

All clinical and biochemical features of GHD children and control subjects are shown in Table 1.

3.1. GHD subjects at baseline vs. control subjects

Height, bone age, GH and IGF-I levels were significantly lower in GHD subjects than controls, as expected (Table 1). No significant difference in mean CCT values (535.7 ± 17 *vs.* 536.2 ± 12.5 μm; $p = 0.859$) was found (Fig. 1A). Similarly, no difference was found in IOP values (12.5 ± 0.8 *vs.* 12.3 ± 0.5 mm Hg; $p = 0.118$) between the two groups.

3.2. GHD subjects after 12 months of GH therapy vs. baseline

A significant increase in height, BMI and bone age was documented in GHD children after 12 months of therapy, as expected. Similarly, IGF-1 levels showed a significant increase (251.8 ± 100.8 *vs.* 90.34 ± 39.34; $p < 0.001$) in all GHD subjects from baseline to 12 months of therapy.

The analysis of the ocular parameters showed a significant increase in mean CCT values (564.7 ± 13.1 *vs.* 535.7 ± 17 μm; $p < 0.001$) in GHD children after 12 months of GH therapy than baseline values (Fig. 1B), with a concomitantly higher corrected mean IOP (15.6 ± 0.7 *vs.* 12.5 ± 0.8 mm Hg; $p < 0.001$).

No significant correlations among CCT at 12 months or the variation (delta) of CCT from baseline to 12 months of treatment and auxological (height SD, height velocity SD, BMI, bone age) and biochemical parameters (IGF-I SD) after 12 months or their delta were found (all $p > 0.05$; data not shown). Conversely, a significant inverse correlation was found between baseline CCT and its delta (Rho −0.656; $p < 0.001$). Grouping all children into those with lower (<the median value of 534 μm) and greater (≥the median value of 534 μm) baseline CCT, we found no significant difference in auxological and biochemical parameters (data not shown).

3.3. GHD subjects after 12 months of GH therapy vs. control subjects

GHD children after 12 months of therapy showed similar BMI, bone/chronological age ratio and IGF-I levels compared to control subjects (all

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