Growth Velocity and Economic Aspects of Human Growth Hormone Treatment in an Egyptian Cohort with Multiple Pituitary Hormone Deficiency: A Retrospective Minireview

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Introduction

Multiple pituitary hormone deficiencies (MPHDs) are defined as an impaired secretion of one or more anterior pituitary hormones in addition to growth hormone (GH), and is a chronic, lifelong condition [1]. Recombinant human GH (hGH) therapy is the ideal therapy for short stature in children with isolated GH deficiency and can effectively increase height gain to reach adult heights within the target range [2], [3]. Although many articles have focused on the causes of hypopituitarism, very few were concerned with children and adolescents, and the exact pituitary hormone profile of MPHD and their response to hGH remains unclear. GH therapy is very expensive and most of the costs are covered by public health insurance or reimbursed by governments in many countries including Egypt [4]. Little is known about the economic aspects versus efficacy of hGH treatment in this specific group of patients.

Therefore, the aim of this study was to analyze the hormone profiles and the characteristics of a cohort of Egyptian children and adolescents with different MPHD etiologies, to assess the growth velocity (GV) during hGH treatment over 1 year in these children and to investigate the possible factors that might affect their height gain. This could result in a better understanding of the characteristic hormone deficits and the effect of hGH treatment in children and adolescents with MPHD.

Methodology

Patients

This study received approvals from the Medical Ethics Committees of Cairo University School
of Medicine and the health insurance endocrine clinic and complied with the guidelines of the Declaration of Helsinki. Verbal assent was received from older patients and written informed consent was obtained from their parents/legal guardians. This is considered a pilot study for another larger study which will include children with a variety of GH deficiency disorders.

This retrospective study was carried out by reviewing the clinical and anthropometric data of 18 Egyptian children and adolescents (eight females and ten males) with a mean age at diagnosis of 10.85 ± 3.87 years. Mean chronological age (CA) at the beginning of the study was 13.44 ± 4.66 years. The children were diagnosed with MPHD at the pediatric endocrine outpatient facilities of three major regional Health Insurance Endocrine Committee Clinics from March 2015 to March 2016. The exclusion criteria included a history of dementia, encephalitis, stroke and other neurological or psychiatric diseases, and children with inadequate replacement for other hormone deficiencies.

The diagnosis of MPHD was based on the following criteria: (1) GH deficiency (GHD); (2) associated deficiency in one or more pituitary hormones (thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], and anti-diuretic hormone [ADH]). The most frequent additional deficiencies were in TSH (ten patients) and gonadotropins (seven patients) with only one patient having ACTH deficiency. Only patients with complete data including magnetic resonance imaging (MRI) results were included in the study. The pituitary axis was examined using the following tests. (1) GHD was diagnosed in the absence of a significant peak in GH secretion (GH peak levels <10 ng/ml) following two different GH provocation tests (the ITT [insulin tolerance test; 0.1 IU/kg (0.2 for obese) regular insulin and the clonidine test; 125 micrograms/m²]). Insulin (0.1 IU/kg) was administered as an intravenous bolus at time 0 to induce a fall in the blood glucose level to 50 mg/dl or less (or one-half of the baseline glucose level). Blood samples were obtained immediately before injection (0) and at 15, 30, 45, 60, 90, and 120 min after injection. Females without any signs of puberty at age ≥10 years and males without any signs of puberty at age ≥11 years were primed with sex hormones before GH testing. Basal cortisol at 60 min was also assessed after insulin stimulation. (2) TSH deficiency was defined as low serum free T4 (FT4 <12.0 pmol/l) (reference range, 12.0–22.0 pmol/l) with concomitantly normal or decreased serum TSH (reference range, 0.27–4.2 μIU/ml) [5]. (3) ACTH deficiency was diagnosed by either decreased serum morning cortisol (COR) level (COR<138 nmol/l) or an impaired cortisol serum concentration rise (COR <550 nmol/l) during insulin-induced hypoglycemia with an inappropriately low serum ACTH concentration [6]. (4) For patients whose age was above 12 years at the time of their first visit, we recorded pubertal development. Gonadotropin deficiency was based on the gonadotropin hormone-releasing hormone-stimulation test (triptorelin 2.5 μg/kg, with a maximum dose of 100 μg, was administered by subcutaneous injection and blood was drawn at intervals beginning 30 min and ending 2 h after injection). A prepubertal response includes a low LH level with FSH predominance (i.e., FSH peak > LH peak). International guidelines suggest a peak LH of >5 IU/L, and/or stimulated LH:FSH ratio of > 0.66 as a cutoff for pubertal response during LHRH testing [7]. The test was performed after overnight fasting.

**Anthropometric measurements**

Height was measured by the same well-trained medical staff using Harpenden stadiometer and expressed in cm. Height measurements were standardized to age and sex and were expressed as standard deviation scores (SDS) relative to the CA, according to the growth charts for Egyptian children and adolescents (2008). Genetic target height was calculated according to the following formula: [(height of the father + height of the mother)/2] cm for girls and +13 cm for boys. Target height measurements were also standardized to age and sex and were expressed as SDS, according to the growth charts for Egyptian children and adolescents (2008) [8]. Weight was measured in the morning, in the fasting state, at every visit, and expressed in kg. Body mass index (BMI) was calculated as weight (kg) divided by height squared (meters). BMI values were transformed into BMI SDS, based on the Normative Values for Egyptian Children and Adolescents (2008) [8], to minimize the confounding effects of age and sex.

**Imaging**

Bone age (BA) was determined by a single observer using a left hand-wrist radiograph and evaluated by Greulich and Pyle’s standards [9]. BA delay, delta BA, and estimated mature height were derived. Hypothalamus-pituitary MRI was performed and the images were reviewed by an experienced radiologist and evaluated for the central nervous system abnormalities. Consensus was reached on the positive nature of MRI findings.

GH therapy was started and maintained for cases at a dose of 0.02 mg/kg/d given daily as 5–6 injections/week preferably at night. Throughout the therapeutic period, patients were evaluated every 3 months for growth response, body weight, and dose readjusted according to the weight increase and response to treatment.

**Cost-effectiveness calculation**

Markov cost-effectiveness simulation model was applied to identify the cost in dollars for a 1 cm
height gain and to treat one patient for 1 year [10].

The hGH therapeutic dose (units/day) was converted to mg/day then calculated per year. Since 1 mg of hGH (trade name in Egypt: Somatropin) costs 1 dollar, we divided by the height gain in cm/year to convert the cost to dollar/cm. Cost-effectiveness considered only the cost of GH therapy. It did not include costs for initial evaluation, follow-up investigations, or medical assessments.

Statistical analysis

The SPSS software 25 computer program was used for data analysis. The descriptive statistics of quantitative variables were presented as mean ± standard deviation, range, frequencies, and qualitative data as percentage (%). For comparison of two groups, the Student’s t-test for dependent and independent variables was used. For comparison of more than two groups, analysis of variance (one-way) was used and followed by post hoc test when significant. The threshold for statistical significance was set at 0.05.

Results

Data from 18 children with MPHD (GH, TSH, gonadotropin, and ACTH deficiencies) were collected, positive consanguinity was present in 10 patients (55.6%). Peak GH levels after clonidine and insulin were 4.06 ± 2.61 ng/ml and 5.39 ± 4.2 ng/ml, respectively. GH was received in a dose of 0.95 ± 0.5 mg/day (range = 0.47–1.67 mg/day and median = 0.93 mg/day). The predicted adult heights on the first and last visits and delta predicted adult height between the first and last visits were 155.78 ± 10.15, 156.71 ± 7.22, and 0.93 ± 4.64 cm, respectively. Computed tomography (CT)/MRI findings were present in 77.8%. Height gain during the study period was 3.5 ± 0.47 cm/year with a 1-year cost of 346.07 ± 183.42 US dollars/patient (range = 171.76–608.33 and median=340.66 dollars/patient). The cost for a 1 cm height gain was therefore 98.87 ± 52.4 US dollars (1 US dollar = 15.7 EGP).

Multiple regression analysis showed that height SDS at presentation and dose of GH (mg/kg/d) contributed significantly to height gain during the period of the study (p = 0.0001, B=0.85 and p = 0.0001, B=1.23, respectively).

Table 1 shows the comparison between males (n = 10) and females (n = 8). Height SDS at presentation was significantly lower (p = 0.003), while BA delay (p = 0.0001) and prepubertal (n = 6) children. The duration of GH therapy before the study (p = 0.01), change in height SDS (p = 0.01), change in BMI (p = 0.005), BA at presentation, and BA delay (p ≤ 0.0001 and 0.049, respectively) was significantly higher while GH dose was significantly lower in the pubertal (p < 0.0001) than in the prepubertal group.

Table 2: Comparison between prepubertal and pubertal patients with multiple pituitary hormone deficiencies

| Variable | Prepubertal (n = 6) | Pubertal (n = 12) | p   |
|----------|---------------------|------------------|-----|
| Age (years) | 8 ± 4.36            | 16.16 ± 8.33     | <0.0001*|
| Age at diagnosis (years) | 6.5 ± 3.83          | 13.03 ± 1        | <0.0001*|
| Duration of therapy (years) | 2 ± 1.09            | 4.13 ± 0.59      | 0.0001*|
| Peak GH by clonidine (ng/ml) | 4.68 ± 3.02         | 3.76 ± 2.47      | 0.49 |
| Peak GH by insulin tolerance test (ng/ml) | 6.1 ± 5.04          | 5.52 ± 3.61      | 0.62 |
| Height at presentation (cm) | 101 ± 16.81         | 130 ± 9.41       | 0.0001*|
| Height SDS at presentation (ng/ml) | −3.1 ± 0.1          | −3.54 ± 0.68     | 0.13 |
| Delta height (cm) | 2.9 ± 1.2            | 3.8 ± 2.92       | 0.48 |
| Delta height SDS | −0.6 ± 0.32         | −0.42 ± 0.24     | 0.01* |
| Target height (cm) | 159 ± 4.71          | 158 ± 3.83       | 0.83 |
| Target height SDS | −1.45 ± 0.27        | −1.4 ± 0.77      | 0.88 |
| Total cost of GH therapy (US dollars) | 243 ± 146.65        | 441 ± 90.52      | 0.004* |

Table 2 compares between pubertal (n = 12) and prepubertal (n = 6) children. The duration of GH therapy before the study (p = 0.0001), change in height SDS (p = 0.01), change in BMI (p = 0.005), BA at presentation, and BA delay (p ≤ 0.0001 and 0.049, respectively) was significantly higher while GH dose was significantly lower in the pubertal (p < 0.0001) than in the prepubertal group.

Discussion

We categorized patients into good or poor responders depending on an increase in height of < 0.7 SDS or > 0.7 SDS in the year, respectively [11]; 12 out of 18 patients showed poor response.
Variability in the clinical presentations and the different anterior pituitary hormone deficiencies is common in patients with MPHD [12]. Studies on the effects of hGH on GV of this group of patients are scarce. In addition, no recent studies have discussed the cost of hGH to treat patients with this condition. In this retrospective study, GV measurements were detected in 18 patients with MPHD; our analysis included 1-year follow-up, performed at regular 3 monthly intervals, by the same physician. Various observations were derived from this study.

Although there were more males (55.5%) than females in the study and boys were younger than girls at the beginning of therapy, the difference was not statistically significant. However, a significantly greater height deviation was observed in female patients. The previous reports indicated a clear gender bias for the referral and treatment of short stature in boys than in girls in spite of equal representation of this condition in the two sexes [13]. This reflects a societal expectation for greater stature in males and explains why girls are more likely to be referred at greater height deviations.

Patients with short stature receive hGH to increase their linear heights. The CAs of MPHD patients receiving hGH in our study were relatively greater than those mentioned in the previous studies [14], [15]. A large number of patients were from rural areas with undeveloped economies, in which the attention to growth disorders is low. On the other hand, Egyptian parents tend to be more familiar with the concept of “delayed puberty”, leading to the older age of presentation to endocrine clinics and contributing to the advanced age of MPHD children and adolescents in our cohort.

The analysis of factors affecting linear growth in children with MPHD showed that children on higher doses of hGH and those with greater height deviation at presentation grew better on hGH therapy compared to others. This concurs with findings of Dahlgren et al. [16] who reported that younger age at starting treatment and a greater difference in current height versus parental height at the start of treatment were good prognostic factors for height gain. Moreover, age of onset of therapy and target height-height SDS was identified as significant predictors of growth in a large sampled study performed on Egyptian children [17].

Researchers reported better height gains in children with MPHD than in those with isolated GHD [18]. In our patients, although the 1-year height gain of 3.5 ± 0.47 cm in the hGH-treated MPHD patients was low, it enabled the children to closely approach their mid-parental height SDS without acceleration of their BA in relation to CA. These data reinforce the positive effect of hGH therapy on linear growth in children with MPHD. The low GV observed in our study could be attributed to poor compliance to hGH therapy. Potential contributing factors to non-adherence should be considered, including fear of needles, discomfort associated with injections, poor knowledge of the condition, and inadequate family support with hGH administration for children, among others [19].

Although, endocrinologists prescribing hGH treatment are increasingly confronted with the question of whether the disadvantages of short stature and the benefits of the intervention justify its cost, our data reinforces the positive effect of hGH therapy on linear growth in children with MPHD in spite of the high estimated cost. Attempts to limit costs in our protocols of management included targeting of dosage-by-weight treatment earlier in childhood and cessation of treatment at a “normal” rather than “maximum” height, both of which were designed to avoid years of high-dose and high-cost therapy during adolescence [20], [21].

The estimated costs of hGH in our patients were higher than the cost in a study of cost-effectiveness/utility of somatropin in the treatment of GH deficiency (GHD) in children. This study designed a decision-analytic model of the epidemiology and treatment of GHD. Treatment of GHD was assessed in two hypothetical cohorts comparing no treatment and treatment with somatropin (0.03 mg/kg/day) for ages 5–16 years and 3–18 years. Costs included those related to drug acquisition, endocrinologist consultations, and primary care office visits. Cost-effectiveness/utility was estimated over patients’ expected lifetimes, and was stated alternatively as discounted (3% per annum) US dollars per normal height year gained and cost per quality adjusted life-year gained. Multivariate sensitivity analyses were conducted to ensure accuracy of the model. It found that cost-effectiveness and cost-utility of treating children from ages 5 to 16 years with somatropin were estimated at approximately 8900 US dollars per normal height gained. Corresponding ratios pertaining to treatment of children from ages 3–18 years were 9300 US dollars per normal height gained. For both age cohorts, the cost-effectiveness/utility of somatropin in the treatment of GHD compares favorably to well-accepted threshold values; thus, the authors concluded that the use of hGH represents reasonable value for money for the treatment of GHD in children [22].

Our estimated cost for hGH was also relatively higher than in another cohort study of 10-year-old prepubertal boys with idiopathic short stature (ISS) treated with GH to estimate the cost-effectiveness of hGH therapy based on the efficacy data used for FDA approval of this indication. That study estimated that direct medical costs including pharmacy, physician, laboratory, and radiologic costs for both the GH-treated group and the no-intervention group as follows: GH cost/mg=52 US dollars; cost of physician visit=58 US dollars; bone-age radiograph=17 US dollars; free thyroxine and thyrotropin measurement=74 US dollars; and IGF1 determination=27 US dollars. Indirect costs such as transportation and parental wages lost because of physicians’ visits were not included in the study [23].

Regardless of the potential for hGH treatment, an initial evaluation is necessary for all children to
identify possible organic causes of poor growth. Their cost-effectiveness calculation for the incremental cost-effectiveness ratio for hGH treatment of ISS was defined as the incremental cost of hGH treatment divided by its incremental clinical benefit in dollars/inch. Moreover, an older study found that the estimated incremental cost-effectiveness of hGH therapy for ISS is about 52,000 US dollars/inch (per 2.54 cm) with GH dose=0.06 mg/kg/d. With an incremental height gain of 1.9 inches (4.8 cm) during 5 years and an incremental cost per child of 99,959 US dollars, this is substantially higher than a previously cited cost estimate of 35,000 US dollars per inch, which was not generated by formal economic analysis and was developed before the availability of the recent efficacy data. The latter study was the first formal analysis of the cost-effectiveness of GH therapy for ISS that used data from the clinical trials that were the basis for the FDA approval [24]. In another study, the authors reported that the annual cost for one child weighing 30 kg was about 15,000-20,000 US dollars [25]. Treatment costs of adolescents using higher “pubertal” doses to maximize adult height might exceed 50,000 US dollars/year and each inch of adult height gained is estimated to cost about 35,000 US dollars [26]. Thus, treating even a 10% fraction of children potentially eligible under the ISS indication (i.e., 0.1% of the childhood population) would cost hundreds of millions of dollars annually [27].

Our reported observations are considered the first analysis of this group of patients (MPHD regarding height gained using hGH and its estimated cost. Given the strong impact of governmental funding on treatment decisions, the clinical criteria for hGH eligibility in patients with MPHD must be carefully considered and based on solid evidence.

Limitations

Our study had some limitations, in particular relating to the limited number of patients included and the relatively short period of follow-up. Therefore, more data in patients with MPHD and a longer duration of treatment and observation are needed. In addition, because of the retrospective nature of the study, MRI data were unavailable for many patients which meant we had to exclude these patients. These limitations should be addressed in the future studies. The generalizability of the present study is also limited by the genetic characteristics which may be different from those of other populations. Moreover, quality of life, adherence, and compliance to hGH were not evaluated which is an important parameter when assessing the cost-effectiveness of a particular treatment.

Conclusion

In this study, patients with MPHD treated with hGH showed improvement in height after 1 year of the treatment. These findings do not indicate that hGH should be used routinely to treat children with short stature due to MPHD, because the treatment should be limited to patients with height 1 SD below their MP-Ht-SDS. Treatment of this group of children appears to be more rewarding if initiated at a younger age. Finally, any benefit derived from an increase in height must be weighed against the risk of adverse events, the cost, and the discomfort of hGH injections. GV during hGH treatment was higher among females than males with MPHD. Height at presentation and GH dose seems to be effective predictors for height gain in patients with MPHD.

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