Children with isolated growth hormone deficiency: Empty sella versus normal sella

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BACKGROUND: Empty sella (ES) may be associated with variable clinical conditions ranging from the occasional discovery of a clinically asymptomatic pouch within the sella turcica to severe intracranial hypertension and rhinorrhea. The need for replacement hormone therapy in ES, as in other syndromes that may cause hypopituitarism, must be assessed for every single hormone, including growth hormone (GH).

AIM: To determine whether or not the presence of ES could allow some changes in the GH responses of the isolated growth hormone deficiency (GHD) patients.

MATERIALS AND METHODS: We included a cohort of 59 short stature children and adolescents with isolated GHD. According to computed tomography finding, they were classified into 2 groups: Group 1 included 40 children with normal sella and 19 children with ES in Group 2. All patients received recombinant human growth hormone (rhGH) with a standard dose of 20 IU/m²/week.

RESULTS: The baseline results were not significantly different for all variables except weight standard deviation was smaller with statistical significant difference (P = 0.02). We identified no significant differences when comparing both groups, except for height standard deviation (HTSD) after the first year of therapy which revealed significant difference in favor of group 1. When comparing pre- and the two post-treatments HTSD results of the studied cases, all showed significant changes after GH therapy. The results of related variables pre-and post-treatment in both the groups showed significant improvement in all variables of the two groups of the study.

CONCLUSION: Our study showed a similar stature outcome in the two treatment groups.
In children, radiological incidence of primary ES was reported as 1-48% with a male-female ratio of 1.4:1.0.\[4\] PES may be associated with variable clinical conditions ranging from the occasional discovery of a clinically asymptomatic pouch within the sella turcica to severe intracranial hypertension and rhinorrhea.\[5\] The need for replacement hormone therapy in PES, as in other syndromes that may cause hypopituitarism, must be assessed for every single hormone, including growth hormone (GH).\[6,7\] Shulman et al. reported 24% of children undergoing CT scanning for evaluation of GHD had an ES,\[8\] Cacciari et al. reported an incidence of 8.8% in cases of isolated GHD.\[9\] In children with isolated GHD, although anatomical abnormalities of the genes involved in the GH axis increasingly recognized, many cases of GHD do not have a well-defined etiology and are classified as idiopathic. The aim of our study was to determine whether or not the presence of ES could allow some changes in the GH responses of the isolated GHD patients.

**Materials and Methods**

In the present study, we included a cohort of 59 short stature children and adolescents with idiopathic GHD. According to CT finding, they classified into 2 groups: (group 1) included 40 children with normal sella and 19 children (group 2) with ES. They were selected over 2 years period. All patients were referred from different schools all over Egypt to the GH National Committee of the school health insurance, where they were diagnosed, provided by GH and followed in association with the growth unit of the Diabetes Endocrine Metabolism Pediatric Unit (DEMPU), Children Hospital, Cairo University. They were subjected to GH treatment for a minimum period of 1 year and a maximum of 2 years.

All patients had the inclusion criteria of a stature more than 2 SD below the mean and if available, a growth velocity (monitored over 6-12 months) below the tenth centile for age and sex. All patients had peak GH level below 10 ng/ml by two provocation tests (Clonidine and insulin tolerance tests). Patients with short stature due to chronic systemic disease, malnutrition, Turner syndrome, bone dysplasias or prenatal causes, or their CT finding revealed an acquired space occupying lesions such as brain tumor, cyst or hydrocephalus or patients showed either atrophic sella or a hypoplastic pituitary gland diagnosed by cranial CT scan, were excluded.

**Methods**

Informed consent was taken from the parents of children; then all cases were subjected to the following. Full history taking and clinical examinations were done. Full anthropometric assessment was also done. Height was measured twice and neared to the next millimeter using Harpenden Stadiometer, height velocity in cm/year is the variable that describes the patient’s 1-year velocity and plotting it in the mid-year interval. Sitting height was also measured using Harpenden sitting height apparatus. Lower segment was calculated by subtraction of sitting height from height, and then from these two measurements, upper to lower segment ratio was derived (US/LS). Weight of the patients was measured using electronic balances and recorded in decimal of kilogram. Puberty was assessed by rating the breast development in girls, genital developments in boys, pubic and axillary hair development in both sexes, according to Tanner’s classification.\[11\] All anthropometric procedures were performed at baseline before treatment and at follow-up by the same observer at the same time of the day (9 a.m.-1 p.m.) in the growth clinic of (DEMPU).

Age-related normal standards for GHD patients were calculated from tables of Tanner and Whitehouse.\[12\] Skeletal maturity was determined by the same observer from an X-ray of the left wrist and hand (Tanner Whitehouse no. 2 method). Laboratory investigations included the following:

1. Thyroid profile (FT3, FT4, Thyroid stimulating hormone [TSH]) was done to exclude primary or secondary hypothyroidism as a cause of short stature. TSH was estimated by immunoradiometric assay (IRMA), while FT3 and FT4 were estimated by radioimmunoassay kits from Diagnosis Product Corporation, (Los Angeles, CA, USA.)
2. Routine general laboratory tests, if needed, which include complete blood picture, renal and liver function tests
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3. GH secretion by two provocation tests (clonidine and insulin tolerance test) separated by 1-week interval and analysis by IRMA. Dose of clonidine given before test was 0.15 mg/m² orally, while that of insulin was 0.1 U/kg I.V. Blood samples were drawn at 0, 20, 40, 60, 90, 120 and sometimes at 180 min if hypoglycemia was delayed. Basal cortisol and at 60 min were also, assessed after insulin stimulation. Patients in pubertal age were primed with sex hormones prior to GH testing. Ethinyl estradiol was given in girls at a dose of 20 μg 3 times/day for 3 days, and in boys testosterone was given at a single dose of 100 mg 3 days preceding the test.

4. Insulin like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) were determined at diagnosis, by solid phase IRMA, using kits from Diagnostic System Laboratories Inc., (Webster, TX, USA). DSL-5600 IGF-1 (IRMA) was included in a sample extraction step in which IGF-1 was separated from its binding protein in serum. This step is considered to be essential for accurate determination of IGF1.[13,14]

**Treatment protocol**

All patients received biosynthetic GH therapy. All patients received rhGH with a standard dose of 20 IU/m²/week. The calculated dose per week was divided for 6 days and given subcutaneously at night. Puberty was not induced by giving sex hormones during GH treatment, since the treatment was started relatively late in these patients. All the patients accepted postponing induction of puberty after explanation by the physician.[15,16]

**Follow-up**

Patients were followed for a minimum period of 1 year and for a maximum of 2 years. Every year, the surface area of each patient was calculated, and the dose of GH was adjusted to keep the therapeutic dose at 20 IU/m²/week (equivalent to 0.2 mg/kg/week) for GHD. Response to GH therapy was judged on data obtained from auxological assessment.

Compliance to therapy is continuously verified by more than one parameter, e.g., height velocity, asking the parents about mode of injection and dosing, counting the empty vials and sometimes by analysis of serum IGF-1. The deviation of individual IGF-1 and IGFBP-3 values from the means for age and sex was calculated in standard deviation score (Z score) and subsequently used in statistical analysis. The laboratory of DEMPU, Cairo University children’s Hospital, provided the mean values for IGF-1 and IGFBP-3.

**Statistical analysis**

The SPSS software computer program was used for data analysis. Quantitative data were presented as mean ± SD, range, frequencies, and qualitative data as percentage. For comparison of two groups, Student's t-test for dependent and independent variables was used when normally distributed and Mann Whitney U-test for independent samples when not normally distributed. The Wilcoxon signed-rank test is a non-parametric statistical hypothesis test used when comparing repeated measurements on a single person to assess whether their population mean ranks differ (i.e., it's a paired difference test). For comparing categorical data, Chi-square (χ²) test was performed. Exact test was used instead when the expected frequency is <5.

**Results**

Descriptive data are presented in Table 1 for the studied cases. The study included 59 isolated GHD children; they were classified into 2 groups: 40 patients with normal sella (group 1) and 19 patients with empty sella (group 2).

**Table 1: Descriptive statistics of the studied patients**

| Item                      | 1=CT normal | 2=Empty sella | Total | Exact sig. (2-sided) |
|---------------------------|-------------|---------------|-------|----------------------|
| 1=Male                    | 25          | 15            | 40    | 0.037*               |
| 2=Female                  | 15          | 4             | 19    | 0.149                |
| 1=Pre-pubertal            | 17          | 11            | 28    | 0.238                |
| 2=Puberty                 | 23          | 8             | 31    |                      |
| 1=No consanguinity        | 14          | 9             | 23    |                      |
| 2=Positive consanguinity  | 26          | 10            | 36    |                      |
| Total                     | 40          | 19            | 59    |                      |

**Item**

| Age at onset (year)       | 1=CT normal | 2=Empty sella | Mean (age) | Standard deviation | Sig. (2-tailed) |
|---------------------------|-------------|---------------|------------|--------------------|----------------|
| 1                         | 8.17        | 3.58          | 0.538      |
| 2                         | 7.68        | 3.25          | 0.852      |
| Age at therapy (year)     | 1=CT normal | 2=Empty sella | Mean (age) | Standard deviation | Sig. (2-tailed) |
| 1                         | 11.41       | 3.56          | 0.852      |
| 2                         | 11.25       | 3.58          | 0.475      |

Duration of delay of treatment (year)

| 1=CT normal | 2=Empty sella | Mean (age) | Standard deviation | Sig. (2-tailed) |
|-------------|---------------|------------|--------------------|----------------|
| 1           | 3.24          | 2.02       | 0.475              |
| 2           | 3.57          | 1.95       |                     |

*Significant difference, CT: Computed tomography
ES (group 2). Group I included 40 patients 25 (62.5%) males and 15 (37.5%) females. Their CA at onset of therapy was 11.2 ± 3.7 years and 11.1 ± 3.8 respectively. Group 2 included 19 patients 17 (89.5%) males and 2 (10.5%) females. It showed a significant difference for sex distribution. Their CA at onset of therapy was 11.3 ± 3.8 years and 10.9 ± 2.76 respectively. There was no significant difference between number of pre-pubertal and pubertal patients in both groups. The duration of delay of treatment (years) was 3.2 ± 2.02 and 3.5 ± 1.95 years in both groups respectively.

Table 2 shows basal auxological and laboratory data. The baseline results were not significantly different for all variables except weight standard deviation was smaller with statistical significant difference (P = 0.02). These indicate the homogeneity of the study groups. Bone age at onset of GH therapy was 7.3 ± 3.9 and 8.8 ± 3.6 years respectively with no statistical difference. In general there was no statistical difference in all items between both groups. Follow-up was achieved for 59 patients in the first year and 29 patients in the 2nd year.

Follow-up is presented in Table 3, only 23 patients from group 1 and 6 patients from group 2 completed the study. Growth response after first year of therapy: Height SDS was improved to – 3.32 ± 0.91 and to – 3.38 ± 0.92 in group 1 and 2 respectively. By the end of the 2nd year height SDS was decreased to – 3.06 ± 1.08 and – 3.08 ± 1.63 respectively. The growth velocity of group 1 was decreased from 4.45 ± 3.25 SDS after a year of therapy to 2.87 ± 2.92 SDS after 2 year of therapy. Group 2 cases their growth velocity decreased from 5.20 ± 4.38 SDS after a year of GH therapy to 4.76 ± 6.24 SDS after 2 year of GH therapy. IGF-1 SDS was decreased from 0.75 ± 0.87 to 47 ± 0.97 at the end of therapy for group 1 patients. In group 2 it raised from 0.03 ± 0.50 to – 0.03 ± 1.50 after 2 years of GH therapy. Also, IGFBP-3 SDS was raised from 0.75 ± 1.92 to 0.75 ± 1.27 in group 1 and increased from – 0.80 ± 3.94 to 0.69 ± 2.16 in group 2. An independent t-test identified no significant differences when comparing both groups, except for height standard deviation (HTSD 1) after the first year of therapy, which revealed significant difference in favor of group 1.

When comparing pre-and the two post-treatments HTSD results of the studied cases, all showed significant changes after GH therapy [Table 4]. Table 5 shows the results of related variables pre- and post-treatment in both groups. Significant improvement was observed in all variables of the two groups of the study.

**Discussion**

The clinical picture in patients with PES is often quite complex and not always possible to dissect symptoms and biochemical findings that are the consequences of the ES from those casually found that are merely the

### Table 2: Basal auxological and laboratory data

| Item                  | 1=CT normal | 2=Empty sella | Mean       | Standard deviation | Sig. (2-tailed) |
|-----------------------|-------------|---------------|------------|--------------------|-----------------|
| Bone age (year)       |             |               | 7.61       | 3.92               | 0.20            |
|                       | 2           |               | 8.21       | 3.94               |                 |
| CABA1                 | 1           |               | 2.33       | 1.42               | 0.32            |
|                       | 2           |               | 1.94       | 1.11               |                 |
| Height (SDS)          | 1           |               | -4.03      | 1.04               | 0.65            |
|                       | 2           |               | -4.11      | 1.00               |                 |
| Weight (SDS)          | 1           |               | 0.23       | 1.82               | 0.00            |
|                       | 2           |               | -3.13      | 2.52               |                 |
| WT/HT                 | 1           |               | 0.53       | 2.12               | 0.02            |
|                       | 2           |               | 0.51       | 3.14               |                 |
| US/LS                 | 1           |               | 0.6564     | 1.70615            | 0.28            |
|                       | 2           |               | 0.9474     | 2.22370            |                 |
| IGF-I                 | 1           |               | 188.33     | 74.26              | 0.58            |
|                       | 2           |               | 179.71     | 85.27              |                 |
| IGF-I (SDS)           | 1           |               | -0.75      | 0.87               | 0.84            |
|                       | 2           |               | -0.70      | 1.53               |                 |
| IGFBP-3               | 1           |               | 27111.19   | 1071.04            | 0.23            |
|                       | 2           |               | 2475.05    | 970.79             |                 |
| IGFBP-3 (SDS)         | 1           |               | -0.75      | 1.92               | 0.43            |
|                       | 2           |               | -0.80      | 3.94               |                 |

CT: Computed tomography, WT: Weight, HT: Height, SDS: Standard deviations, US: Upper segment, LS: Lower segment, IGF-I: Insulin like growth factor-1, IGFBP-3: Insulin like growth factor binding protein-3

### Table 3: Follow-up of auxological and laboratory data

| Item                  | 1=CT normal | 2=Empty sella | Mean       | Standard deviation | Sig. (2-tailed) |
|-----------------------|-------------|---------------|------------|--------------------|-----------------|
| SDH1                  | 1           |               | -3.32      | 0.91               | 0.90            |
|                       | 2           |               | -3.38      | 0.92               |                 |
| SDH2                  | 1           |               | -3.08      | 1.08               | 0.76            |
|                       | 2           |               | -3.08      | 1.03               |                 |
| GV1SD                 | 1           |               | 4.45       | 3.25               | 0.16            |
|                       | 2           |               | 5.20       | 4.38               |                 |
| GV2SD                 | 1           |               | 2.87       | 2.91               | 0.25            |
|                       | 2           |               | 4.76       | 6.24               |                 |
| IGF1SD1               | 1           |               | -0.47      | 0.97               | 0.13            |
|                       | 2           |               | 0.03       | 1.50               |                 |
| BP3SD1                | 1           |               | 0.75       | 1.27               | 0.83            |
|                       | 2           |               | 0.76       | 2.16               |                 |
| HT gain first year (SD) | 1       |               | 1.95       | 0.90               | 0.00            |
|                       | 2           |               | 1.03       | 0.37               |                 |
| HT gain second year (SD) | 1    |               | 0.70       | 0.54               | 0.86            |
|                       | 2           |               | 0.65       | 0.55               |                 |
| Second year-start year (SD) | 1   |               | 1.14       | 0.95               | 0.07            |
|                       | 2           |               | 0.40       | 0.48               |                 |

SD: Standard deviation, CT: Computed tomography, HT: Height
reason for referral. During childhood, irrespective of etiology, GHD is characterized by progressive slowing in growth, delayed skeletal maturation and delayed puberty. Indeed, growth failure is the major presenting sign of GHD in children. However, to our knowledge, no studies have been reported so far to allow a detailed therapeutic picture of patients with idiopathic GH deficiency with PES. The aim of our study was to determine whether or not the presence of ES could allow some changes in the GH responses of the isolated GHD patients.

In the present study, the frequency of an ES was significantly high in male than female, this result was in agreement with others. This finding cannot be explained by a conclusive explanation. It is questioned whether this can be answered by genetic factor “the postulated greater vulnerability of male to exogenous insult. There was no significant difference between pre-pubertal and pubertal patients in both groups. Furthermore, there was no significant difference in duration of delay of treatment or the age of starting GH therapy. Our study showed a significant decrease in body weight in group 2. This was in contrast to the result of Del Monte et al. who reported that overweight were frequently recorded in cases with ES.

In children with idiopathic GH deficiency short-term outcome measures (<2 years) must take into account the age, pubertal status, and degree of growth retardation of the individual patient. The change in height SDS will provide the best indicator of response, height velocity SDS, and the change in height velocity (cm/year or SDS) all have utility, and are sometimes superior, in assessing response.

Short-term auxological features showed a successful first year response to GH treatment in individual patients of both groups include a change in height SDS of more than 0.3-0.5, a first-year height velocity SDS of more than +1. All growth variables show insignificant deference between both groups except for HTSD 1 after the first year of therapy which revealed significant difference in favor of group 1. In our study, after the 1st two years of GH treatment, there was no significant difference between cases with or without ES in auxological features. This is due to the similar growth response during the 1st and 2nd year.

Conclusion

This is the first observational prospective study to investigate the outcome of subjects with childhood isolated GHD with or without ES. Our study showed a significant decrease in body weight in case with ES.

| Table 4: Follow-up of height SD for 2 years with growth hormone therapy in both groups |
| --- |
| **N** | **Mean** | **Standard deviation** | **Minimum** | **Maximum** | **Percentiles** | **Test statistics** |
|   |   |   |   |   |   |   |   |
| Normal sella |   |   |   |   |   |   |   |
| SDH0 | 23 | -4.25 | 1.07 | -6.50 | -2.70 | -5.10 | -4.00 | -3.40 | Chi-square | 32.1 |
| SDH1 | 23 | -3.53 | 0.94 | -5.90 | -1.90 | -3.90 | -3.40 | -2.80 | df | 2 |
| SDH2 | 23 | -3.06 | 1.08 | -5.50 | -1.40 | -3.80 | -2.80 | -2.40 | Sig. | 0.000 |
| Empty sella |   |   |   |   |   |   |   |   |
| SDH0 | 6 | -4.11 | 1.49 | -6.00 | -2.00 | -5.4750 | -4.30 | -2.60 | Chi-square | 9.33 |
| SDH1 | 6 | -3.43 | 1.47 | -5.20 | -1.20 | -4.8250 | -3.55 | -2.10 | df | 2 |
| SDH2 | 6 | -3.08 | 1.63 | -4.40 | -1.30 | -4.2500 | -3.85 | -1.50 | Sig. | 0.009 |

SD: Standard deviation, SDH: Standard deviation of height

| Table 5: Pre-and post-growth hormone treatment results in both groups |
| --- |
| **Group** | **SDH1-SDH0** | **SDH2-SDH0** | **IGF1SD1-IGFSD0** | **BP3SD1-BP3SDO** |
|   |   |   |   |   |
| Empty sella | Z | -3.770(a) | -2.201(a) | -2.213(a) | -3.139(a) |
| Sig. (2-tailed) | 0.000 | 0.028 | 0.027 | 0.002 |
| Normal sella | Z | -5.256(a) | -4.045(a) | -2.639(a) | -4.259(a) |
| Sig. (2-tailed) | 0.000 | 0.008 | 0.008 | 0.000 |

Wilcoxon signed ranks test, (a)Based on negative ranks, SDH: Standard deviation of height, IGF1SD: Insulin like growth factor-1 standard deviation, BP3SD: Binding protein-3 standard deviation
However, in our opinion, our group of subjects showed similar clinical characteristics. Our data, in fact, showed a similar stature outcome in the two treatment groups.

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