# The effect of growth hormone treatment on head circumference in growth hormone-deficient children

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SUMMARY: Darendeliler F, Baş F, Gökçe M, Poyrazoğlu Ş, Şükür M, Bundak R, Saka N, Günöz H. The effect of growth hormone treatment on head circumference in growth hormone-deficient children. Turk J Pediatr 2008; 50: 331-335.

The aim of this study was to analyze head circumference (HC) growth retrospectively in longitudinally followed growth hormone (GH)-deficient children on GH therapy. Data of 54 (25F, 29M) children with GH deficiency were analyzed by dividing the children into two groups: Group 1 with height age (HA) ≤5 years (yrs) (n:18) and Group 2 with HA >5 yrs (n:36). Anthropometric measurements were expressed as standard deviation score (SDS) for chronological age (CA), and HC was also expressed as SDS for CA and HA. Group 1, with CA 6.6 (2.9) yrs at onset of therapy, showed an increase in height SDS from –3.8(1.4) to –2.4(1.7) (p<0.001) and in HC SDS for CA from –1.9(1.5) to –1.3(1.6) (p<0.05) on 4.8(3.5) yrs of therapy. Group 2, with CA 12.6(2.2) yrs, increased height SDS from –3.4(1.3) to –2.5(1.4) (p<0.001) and HC SDS for CA from –1.2(1.3) to –1.4(1.2) (NS). HC SDS for HA was –0.4(1.3) in Group 1 and –0.2(1.1) in Group 2 and showed no significant change. When analyzed by quartiles for cumulative dose of GH, HC SDS for HA became 0.08(1.2) in the fourth dosage quartile (p=0.043), not significantly different from the mean. HC is disproportionately small for age but normal for the height. GH treatment results in an increase in HC of the children towards normalization in younger children. An increase in cumulative GH dose is associated with an increase in HC, but this is not inappropriate.

*Key words: growth hormone treatment, growth hormone deficiency, head circumference, children.*

The most apparent metabolic effect of growth hormone (GH) is stimulation of linear growth in children prior to epiphyseal fusion[1]. Head circumference (HC) and hand/foot growth are also GH-dependent; however, it is still controversial whether body proportions of short children treated with GH are affected to the same extent as height. It has been shown that GH therapy leads to a rapid catch-up growth of HC especially in younger patients with GH deficiency (GHD)[1-3]. It is well known that GH excess causes gigantism in children with excess linear growth and acromegalic features[4]. High dose of GH therapy may result in a phenotype similar to features of GH excess[5-7]. On the other hand, long-term use of recommended doses of GH as a part of replacement therapy may also cause acromegalic features.

There are a few studies that have investigated the effect of GH therapy on HC in patients with GHD[3,8,9]. Segal et al.[9] reported that HC of GH-deficient children treated with GH increased disproportionately to height, becoming large for stature. The aim of this study was to investigate the effects of GH therapy on HC in longitudinally followed GH-deficient children on therapy in a retrospective analysis.

## Material and Methods

Fifty-four (25F, 29M) children with idiopathic GHD were included in the study. Diagnosis of GHD was based on auxological criteria and a GH peak <10 ng/ml in response to two GH provocation tests done by standard methods (10) and insulinlike growth factor (IGF)-1 and IGF binding protein-3 (IGFBP-3) measurements

below -2 standard deviations[11]. All patients were on GH therapy. Forty-three patients had isolated GHD and 11 multiple pituitary hormone deficiency (MPHD) who were on appropriate replacement therapy [7 patients were on L-thyroxine (L-$T_4$), 4 patients on glucocorticoid and L-$T_4$, and 4 patients on sex steroid replacement therapy]. Patients with syndromes, dysmorphic features and cranial surgery were excluded from the study.

Height, weight and HC measurements obtained by standard methods[12] were taken from the patient files. Height and weight measurements were expressed as standard deviation score (SDS) for chronological age (CA)[13]. HC was also expressed as SDS for CA and height age (HA)[14,15]. HA was defined as the age at which the subject's height had an SD of zero compared with normal children. GH dose was expressed as cumulative dose in mg for total duration of therapy. Height and HC SDS values were calculated for quartiles of cumulative GH dose. The difference between the HC at onset of therapy and at the last examination was denoted as Δ HC SDS.

the total group. Linear regression was done to analyze the effect of GH therapy on HC controlling for age and gender.

## Results

The mean (SD) CA at onset of GH therapy was 10.6(3.7) yrs and at recent examination was 13.9(3.7) years. Height SDS increased from –3.5(1.3) to –2.5(1.5) (p=0.000) at a mean duration of 3.3(2.8) yrs in all children. The auxological parameters of the patients in Group 1 and 2 are shown separately in Table I. Height at onset of GH treatment was similarly retarded in both the young and older children. HC was also similarly retarded in both groups for CA (p=0.001) but not significantly retarded for their stature. In both groups, height SDS showed a significant increase over therapy. HC SDS for CA showed a significant increase in Group 1 but there was no change for HC SDS for HA. In Group 2, HC SDS did not show a significant change expressed for either CA or HA.

There was no correlation of IGF-1 and IGFBP-3 SDS and HC SDS at onset and at final examination.

**Table I.** Height and HC SDS Values of Groups 1 and 2

|  | Group 1 (n: 18) | | | Group 2 (n: 36) | | |
|---|---|---|---|---|---|---|
|  | At onset | | Final | At onset | | Final |
| CA (yrs) | 6.6 (2.9) | | 11.3 (4.7) | 12.6 (2.2) | | 15.1 (2.3) |
| Height SDS | -3.8 (1.4) | p=0.005 | -2.4 (1.7) | -3.4 (1.3) | p=0.000 | -2.5 (1.4) |
| HC SDS |  |  |  |  |  |  |
| for CA | -1.9 (1.5) | p=0.05 | -1.3 (1.6) | -1.2 (1.3) | NS | -1.4 (1.2) |
| for HA | -0.4 (1.3) | NS | -0.3 (1.3) | -0.2 (1.1) | NS | - 0.5 (1.1) |
| Weight SDS | -2.0 (1.2) | NS | -1.5 (1.5) | -1.8 (0.9) | p=0.048 | -1.5 (1.3) |
| Duration of GH Therapy (yrs) | —— | | 4.8 (3.5) | —— | | 2.6 (2.1) |
| GH dose (total) (mg) | —— | | 1519.3 (2153.5) | —— | | 853.9 (715.0) |

CA: Chronological age. SDS: Standard deviation score. HC: Head circumference. HA: Height age. GH: Growth hormone.

Considering their short stature and that the brain maturation continues in early childhood, children were grouped with respect to their HA as being below or above 5 years. Group 1 consisted of children with HA ≤5 years (yrs) (n: 18) and Group 2 with HA >5 yrs (n: 36).

Statistical analyses: Mean (SD) values are given. Nonparametric tests were used for comparison between the mean values within groups. Pearson correlation was used for linear correlation in

There were no differences in ΔHC SDS between patients using steroid and/or thyroxine compared to patients not using them. However, the number of patients with MPHD was not large. There was no difference in ΔHC SDS in the isolated GHD group (0.16±0.91) and in the MPHD group (-0.17±0.83) (p=0.39).

HC SDS for CA and for HA expressed for quartiles of GH dose are shown in Figure 1. As is evident, HC SDS showed an increase
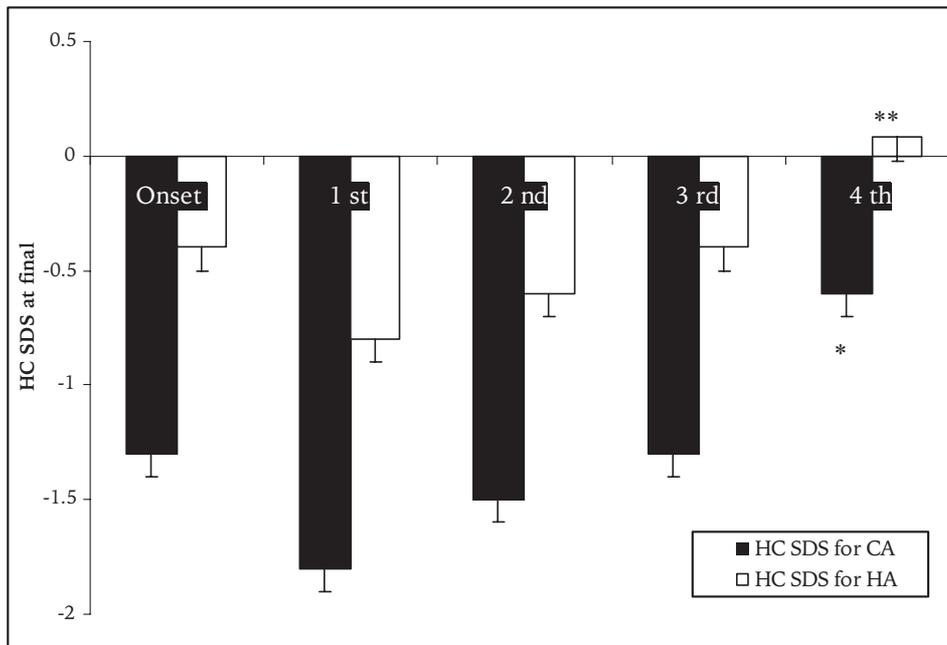
**Fig. 1.** Head circumference standard deviation score (HC SDS) at quartiles for GH dose, *p= 0.006, **p= 0.043.

through the dose quartiles, but becoming significant only in the 4th quartile. There was also positive correlation between Δ HC SDS for CA and cumulative GH dose as shown in Figure 2 controlling for gender and age (r=0.34 and p=0.01). Even if the one child with cumulative GH dose at the upper end is excluded from the analysis, this correlation is still significant (r=0.30, p=0.02). When the correlation was done separately in the two
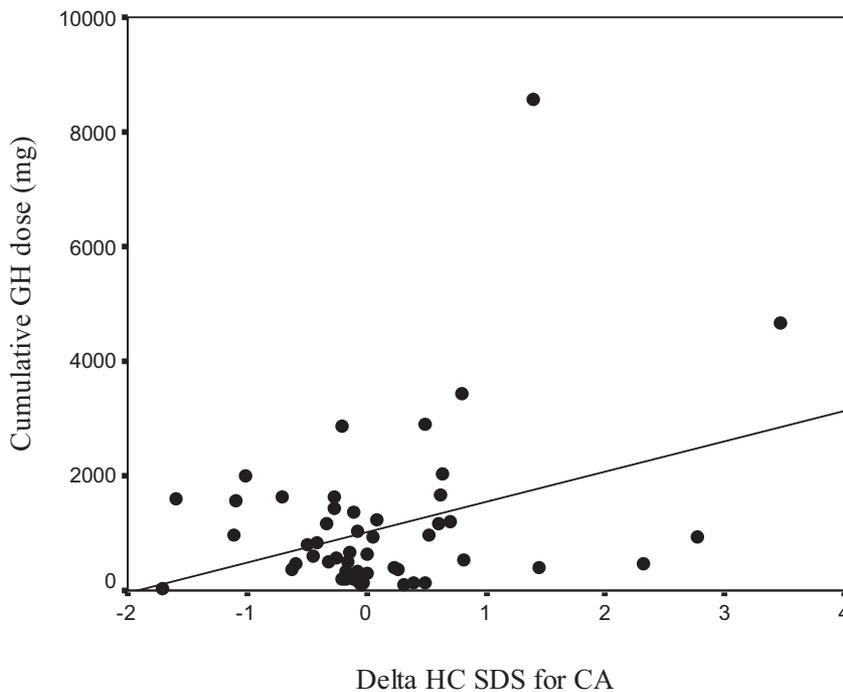


**Fig. 2.** Correlation between Δ head circumference standard deviation score (HC SDS) and cumulative growth hormone (GH) dose (mg).

groups, it was seen that the positive correlation between ΔHC SDS and cumulative dose of GH corrected for age and gender persisted in Group 1 (r=0.42, p=0.03) but not in Group 2.

Δ Height SDS showed correlation with cumulative GH dose (r=0.55, p=0.001). There was no correlation between Δ height SDS and Δ HC SDS.

Controlling for age, gender and duration of therapy, cumulative GH dose remained the only significant parameter in the increase in HC SDS (p: 0.008).

## Discussion

It has been reported that HCs in untreated patients with GHD are disproportionately small[3,9]. Laron et al.[3] showed that in 35 GH-deficient patients, prolonged deficit of GH leads to significant retardation of HC, which was less than retardation in linear height. Segal et al.[9] reported that untreated patients with GHD had small HC for age and HA. HC of our patients was subnormal for their CA, but normal for their height.

Laron et al.[3] reported that treatment with GH leads to catch-up in head growth in young GH-deficient patients (CA <5 yrs) and prevention of further loss in relative head size in the older GH-deficient children (CA >9 yrs). Segal et al.[9] on the other hand showed an increase in HC of children even at older ages and attributed this delayed growth by a composite of cranial vault growth and cranial base growth. In our study, HC showed an increase in younger but not in older children. When adjusted for stature, the increase in HC was not markedly significant even in younger children.

When analyzed with respect to the parameters that have an effect on HC growth, HC growth was associated with cumulative GH dose. Segal et al.[9] reported that in 52 GH-deficient patients on GH therapy, HC growth increased disproportionately to linear growth in dose- and duration-dependent fashion. Clayton et al.[8] also found that HC growth correlated significantly with duration of GH therapy in 14 children with idiopathic GHD. In addition to HC growth, it has been reported in several studies that long-term high-dose GH treatment may result in acromegalic features[4-7]. Acromegalic features like broadening of nasal bridge, large foot size, ankle swelling, and right hip pain in four subjects treated with high GH dose (0.7 mg/kg/week) have been reported[7]. Carvalho et al.[4] reported long-term GH treatment even with standard doses might be associated with acromegalic features in patients with GHD who achieve final height, especially in girls, and neither the clinical nor hormonal parameters were useful to predict the development of these features. In our patients, GH was used in appropriate doses (25-30 μg/kg/day) as recommended in GHD and this dose of GH did not cause an inappropriate increase in HC.

In conclusion, our study showed that HC is disproportionately small for age but normal for height in GHD children. GH treatment results in an increase in HC of the children with GHD towards normalization only in younger children with HA less than 5 years. In older children, there is no increase in HC. Although cumulative dose of GH is associated with an increase in HC especially in younger children, this does not result in an inappropriate increase in HC.

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