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Short Communication

Evaluation of The Efficacy of Long-Term Growth Hormone Therapy in Patients with Hypochondroplasıa

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What is already known on this topic?
Children with hypochondroplasia were given rhGH treatment in a limited number of studies. In these studies, treatment doses of GH and height gain were different.

What this study adds?
In this study presented long term follow up and evaluated the GH therapy responses of the patients with hypochondroplasia by clinical, radiological and genetic examination.high-dose GH therapy may be required for skeletal dysplasia.

Abstract
Hypochondroplasia is a cause of disproportionate short stature and characterized by slight clinical manifestations. The aim of this study was to evaluate the efficacy of long-term GH therapy in hypochondroplastic cases with inadequate response to GH simulation tests . In this study, six patients who had height SDS of -3.43 before the treatment and a mean age of 7.42 and received GH treatment at a dose of 0.2 mg / kg / week for a mean of 4.45 years were evaluated. As a result, a good accepted response was found in the first year in hypochondroplastic patients with findings of GH deficiency, but this increase was not found to be sufficient in the patients who achieved the final height.
Keyword: hypochondroplasia, growth hormone therapy, skeletal dysplasia

Introduction
Hypochondroplasia is a common skeletal dysplasia that has an autosomal dominant transition and clinical manifestations can become evident over time. Disproportionate short stature, macrocephaly, lumbar lordosis, rhizomelic / mesomelic shortness, brachydactyly may be seen (1,2). Clinical manifestations may be evident with increasing age in hypochondroplastic cases. It may appear as normal or almost normal in early childhood and may not be evident until puberty. The final height has been reported to be 146 ± 4.9 cm for males and 137.6 ± 6.3 cm for females (3). The diagnosis of hypochondroplasia can be made clinically, radiologically and genetically. Diagnostic radiological findings include decreased interpedicular distance between L1 and L5 on radiographs and short lumbar pedicles (4). Hypochondroplasia is frequently observed due to the Fibroblast Growth Factor Receptor 3 (FGFR3) mutation locating at 4p16,3. However, mutations in all hypochondroplasia patients may not be observed. Children with hypochondroplasia were given rhGH treatment in a limited number of studies. In these studies, treatment doses of GH and height gain were different. Very little of the GH-IGF-1 axis has been mentioned in the studies performed, and similarly, very few studies have reported final height results following the treatment. In this study, it was aimed to evaluate the GH therapy responses of the patients who met the criteria for growth hormone deficiency at the first presentation and were started rhGH replacement therapy and had definite diagnosis of hypochondroplasia by clinical, radiological and genetic examination.

Methods
In this study, we evaluated the growth of hypochondroplasia patients who had been followed up for long term in our clinic. We evaluated patients who applied to our clinic in between the years 2000 and 2017 with hypochondroplasia and had inadequate response to growth hormone stimulation tests. The height measurements of the cases were evaluated with Harpender ® stadiometer, pubertal staging according to Tanner Marshall, and bone ages with Greulich and Pyle bone age atlas (5-7). The diagnosis of hypochondroplasia was made by clinical anthropometric evaluation (height, sitting height, upper / lower segment ratio etc.), presence of specific

radiological findings (decreased interpedicular distance in vertebral graft, short square iliac bone in pelvis graft, extension in distal fibula), and demonstration of FGFR3 gene mutation if possible. Presence of any affected parents in the family history supported the diagnosis. In all cases rhGH treatment was given at a dose of 0.2 mg / kg / week. IGF-1 and IGFBP3 values, pubertal progression, change in upper / lower segment ratio, bone age progression rate and the achieved final height were assessed in the follow-up of the cases. All participants provided a informed consent taken from the parents and the study protocol was approwed by Ankara University Ethic Committe (approval number :15-638-15)

Results

Six cases (1 male / 6 girls) with an initial mean age of 7.08 years and one in puberty were included in the study. Before the treatment, mean annual height velocity of the patients was 3.96 cm, height SDS was -3.86, bone age was 4.84 years, upper segment/lower segment ratio was 1.34, and specific radiographic findings were found in all cases (Table 1). In the first year of growth hormone therapy, the height velocity was between 6.9 and 10 cm (mean 8.4 cm) and it decreased to 5.5 cm in the third year and to 5.3 cm in the fourth year. At the first year of treatment, the mean height SDS was found to be -3.86, and the Δ height SDS of +0.51 was found to decrease gradually in the following years. On the last follow-up of the cases when they were on 4.45 years of growth hormone therapy; the mean age was 12.48 years, height SDS was -3.57, Δ height SDS was 0.66, bone age was 12.9 years and IGF-1 SD was 1.34. Four of the patients with mean puberty starting age of 10.66 years and non-rapid development of pubertal findings achieved the final height. Of the four patients who achieved the final height; the final SDS was -3.57, Δ height SDS was +0.26 and the upper / lower segment ratio remained at the same level and there was no increase in disproportionality. During treatment, IGF-1 levels did not exceed + 2 SDS and remained in the confidence interval (Table 2).

Discussion

İn the literature, about to the use of growth hormone in skeletal dysplasia are not adequate except for achondroplasia, and usually short-term treatment results have been reported (8). However, the genetic heterogeneity and phenotypic diversity of the diagnostic features lead to different conclusions regarding treatment efficacy. Activating mutations of FGFR3, which have an effect on the negative regulation of cartilage growth, are seen in hypochondroplasia and achondroplasia (9). The N540K mutation is also seen in hypochondroplasia and is associated with more severe shortness and disproportion. However, mutations are not observed in all hypochondroplasia patients (10,11). In one of our cases, 1612 A> G (p.IIE538Val) heterozygous mutation in the FGFR3 gene was detected.

In children with achondroplasia there is a transient increase in height velocity without any effects on final height, and consequently, the use of routine recombinant growth hormone in achondroplasia is not recommended (12). In children with hypochondroplasia, there is no placebo-controlled study of the effects of growth hormone therapy on adult height. Previous studies have shown that the use of growth hormone improves the increase rate of height in children with hypochondroplasia, especially at puberty (13,14). In a study published by Pinto and colleagues in 2014, 40 patients were followed up without treatment and achieved the final height, and 19 patients with hypochondroplasia who were given 0.057 mg / kg / day growth hormone were compared. The height increase rate of 5.1 ± 0.3 cm / year at the beginning of treatment, reached to 8.1 ± 1.9 cm/year in the first year, 6.2 ± 1.7 cm/year in the second and 4.8 ± 2.2 cm/year in the third year. Similarly, the best response was taken in the first year of treatment and decreased in the following years (15). Also, in a meta-analysis published in 2015, effects of growth hormone therapy was evaluated in hypochondroplastic cases. A total of seven publications and 113 patients with rhGH treatment were included in this meta-analysis. Among these patients, 59.7% were male and most of them were pre-pubertal at the beginning of the treatment.

Again in this meta-analysis, the average growth hormone dose is 0,25 mg / kg / week. In all studies, adult height which was predicted at the beginning of the treatment was below the normal level and an increase in the adult height predicted after the rhGH treatment was determined. In the meta-analysis of these seven studies, in the median post-treatment predicted adult height SDSs, there was an increase of 0.414 for the first year, 0.530 for the second year, and 0.609 for the third year. This increase was especially the first year of treatment and continued to decline. However, during the 36th month of treatment, the adult height is still below normal. It was observed that the best rate of height increase under treatment was the first year, suggesting that the effect of treatment on adult height was related to the height achieved for the first year. In our study, at the first year of growth hormone treatment, delta height SDS was +0.51, suggesting that the response to growth hormone treatment was good. However, growth rates in the follow up have decreased. IGF1 levels remained in the confidence interval during treatment. In total, Δ GSDS remained at 0.21 and was interpreted as insufficient response.

During the follow-up, we found that puberty started in the expected normal age and pubertal findings did not accelerate under the treatment of GH. Progression of bone age with GH therapy, which is seen in some skeletal dysplasia, is a finding that is noticeable in terms of effecting the final height (16). In our cases, Δ bone age was found to be 6.6 years at the end of the treatment and the fact that there was not a significant increase was attributed to the accompanying GH deficiency.

An average of 28.5 cm height increase due to the treatment was observed in the 4 patients achieving the final height, and the mean height was found to be 136.47 cm. After treatment, Δ height SDS was found to be +0.2. Upper / lower ratios under growth hormone therapy were not significantly deteriorated, and no side effects were observed. The lack of change in disproportionality in patients with hypochondroplasia after GH therapy is a finding that shows the treatment had no side effect. In patients with hypochondroplasia and GH deficiency, although rhGH therapy has seemed to be reliable, the final height had no improvement with the dose of 0.2 mg / kg / week.

Conclusion

In GH deficient patients with hypochondroplasia, standard dose of GH treatment was found to be sufficient to reach an increase in height just above 0.5 SD in the first year, which is acceptable, but not in the patients who achieved the final height. This finding supports the idea that high-dose GH therapy may be required for skeletal dysplasia. Normal progression of puberty with a standard dose of GH therapy, lack of acceleration of bone age and skeletal disproportion, and IGF-1 level remaining safe in the normal range are consistent with the idea that GH therapy is safe.

References:

1. Meyer MF, Menken KU, Zimny S, Hellmich B, Schatz H: Pitfall in diagnosing growth hormone deficiency in a hypochondroplastic patient with a delayed puberty. Exp Clin Endocrinol Diabetes 2003;111:177–181.
2. Glasgow JF, Nevin NC, Thomas PS: Hypochondroplasia. Arch Dis Child 1978;53:868– 872.
3. Maroteaux P, Falzon P: Hypochondroplasie. Revue de 80 cas. Arch Fr Pediatr 1988;45:105– 109.
4. Rimoin DL, Cohn D, Krakow Det al. The skeletal dysplasias: clinical-molecular correlations. Ann. N Y Acad. Sci. 1117, 302–309 (2007).
5. Greulich WW, Pyle SI.Radiographic Atlas of Skeletal Development of The Hand and Wrist,2nd ed.Stanford,CA: Stanford University Press, 1959
6. Marshall WA, Tanner JM. Variation in the pattern of pubertal changes in girls. Arch Dis Child 1969;44:291–303.

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7. Marshall WA, Tanner JM. Variation in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.
8. Massart F, Miccoli M, Hight outcome of short children with hypochondroplasia after recombinant human growth hormone treatment: a meta-analysis. Pharmacogenomics 2015 ;2015 Nov;16(17):1965-73.
9. Bellus GA, McIntosh I, Smith EA, Aylsworh AS, Kaitila I, Horton WA, Greenhaw GA, Hecht JT, Francomano CA: A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet 1995;10:357–359.
10. Grigelioniene G, Eklöf O, Laurencikas E, Ol- lars B, Hertel NT, Dumanski JP, Hägenas L: Asn540Lys mutation in fibroblast growth factor 3 and phenotype in hypochondroplasia. Acta Paediatr 2000;89:1072–1076.
11. Rousseau F, Bonaventure J, Legeai-Mallet L, Schmidt H, Weissenbach J, Maroteaux P, Munnich A, Le Merrer M: Clinical and genetic heterogeneity of hypochondroplasia. J Med Genet 1996;33:749–752.
12. Horton WA, Hall JG, Hecht JT: Achondroplasia. Lancet 2007;370:162–172.
13. Appan S, Laurent S, Chapman M, Hindmarsh PC, Brook CG: Growth and growth hormone therapy in hypochondroplasia. Acta Paediatr Scand 1990;79:796–803.
14. Ramaswami U, Hindmarsh PC, Brook CG: Growth hormone therapy in hypochondroplasia. Acta Paediatr Suppl 1999;88:116–117.
15. Pinto G, Cormier-Daire V, Le Merrer M, Sa- mara-Boustani D, Baujat G, Fresneau L, Viaud M, Souberbielle JC, Pineau JC, Polak M: Efficacy and safety of growth hormone treatment in children with hypochondroplasia: comparison with an historical cohort. Horm Res Paediatr 2014;82:355–363.
16. Kanaka-Gantenbein C. Present status of the use of growth hormone in short children with bone diseases (diseases of the skeleton). J Pediatr Endocrinol Metab. 2001 Jan;14(1):17-26.

Table -1: The Presentation Features of the Patients

Features	**Presentation Findings**
Gender	5 Female/ 1 Male

Chronological age (year) mean± SD	7,08 (5,1-10,44) ±3,2
Height SDS mean± SD	**-3, 68**(-2,66 -4,87)±0,39
BA (year) mean± SD	**4,84** (2-8.8) ±2,97
Upper/Lower Segment Ratio	**1,34** (1,2-1,6) ±0,2
Affected parent	Mother→ 1 patient Father→ 4 patient No affection→ 1 patient
FGFR3 Mutation	1 patient 1612 A> G (p.IIE538Val) heterozygous mutation
Pretreatment height velocity (cm) mean± SD	3,96 cm ±0,69
THSDS mean± SD	-2,39(between-0,25 and-3,79) ±1,09
IGF-1 SD mean± SD	-1,49 (-0,32 and -2,73) ±0,74
IGFBP3 SD mean± SD	-2,09 (1,08 and -5,7) ±2,1
GH deficiency Partial/Complete	Partial GH deficiency 3 patients Complete GH deficiency 3 patients

Table-2: Characteristics of patients on the treatment cessation

	GH treatment cessation (n:4)
Gender	4 females
Chronological age (year) mean± SD	**13,75** (12,62-14,93) ±0,9
Bone age mean± SD	**14,62** (14-15,5) ±0,75
Upper/Lower Segment ratio mean± SD	1,4 (1,56-1,28) ±0,15
GH therapy duration time mean± SD	**4,43** (3,25-6) ±1,3
Total increase in height (cm) mean± SD	**28,5** (20,4-42) ±11,4
Height SDS mean± SD	**-3,57** (-2,4 and -4,6)±0,84
Delta height SDS mean± SD	**0,20** (-0,91 and1,77) ±1,1
IGF-1 SD mean± SD	**1,18** (-0,67 and 5,34) ±2,7

Mean height mean± SD	136,47 (129,5-144) ±7,3
Predicted adult height/Final height	1.patient:-/129,5cm 2.patient:140,5cm/144cm 3.patient:146,5cm/142cm 4.patient:126,7cm/132,6 cm