

## CASE REPORT

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# Favorable Growth Hormone Treatment Response in a Young Boy with Achondroplasia

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## ABSTRACT

**Background:** Achondroplasia is a skeletal dysplasia, the most common cause of rhizomelic dwarfism. **Case presentation:** This is a ten year old boy who was first diagnosed prenatally. He had a mutation c1138G>A in the gene *FGFR3* in a heterozygotic constellation. His IGF1 and IGFBP3 levels were normal. Two stimulation tests for growth hormone were performed with values within the reference range. His psychomotor development was adequate for his age except for speech difficulty. He started with recombinant hGH (r-hGH) at the age of 3.4 years in a dose of 0.06 mg/kg. His mean Height SDS (HtSDS) was -2.2. **Results:** The growth increased to 10 cm/year in the first year of therapy (HtSDS -1.1). It decreased during the second year to 4 cm (HtSDS -1.7) and again increased during the third year to 8 cm/year (HtSDS-1.3). In the next years the growth was constant (6.5, 2.3, 3.5 cm / year). He is still growing in the 3<sup>rd</sup> percentile of the growth curve (HtSDS - 1.2) under GH treatment. The body disproportion remained the same. **Conclusion:** The growth response on GH treatment was satisfactory in the first 4 years of treatment, and the boy still continued to grow. The young age at the start of treatment was also of importance. Our other patients with achondroplasia who started treatment older had a poor response to growth hormone.

**Key words:** Achondroplasia, skeletal dysplasia, Growth hormone treatment.

## 1. INTRODUCTION

Skeletal dysplasias are common causes of severe growth retardation. Among these disorders, achondroplasia is the most common genetic form of chondrodysplasia in humans and is characterized by short-limb dwarfism, macrocephaly with a prominent forehead, and mid-face hypoplasia (1). Characteristic radiographic findings of the skeleton such as caudal narrowing of the interpedicular distance, small iliac wing, narrow greater sciatic notch, and metaphyseal flaring of tubular bones are usually observed. Average adult height in achondroplasia is, in the Caucasian population, between 112 and 136 cm (mean 124 cm) for women and 118-145 cm (mean 132 cm) for men (2). This disorder is inherited as an autosomal dominant trait, although the majority of cases are sporadic. At the last decade of the past century, studies have revealed point

mutations in the transmembrane domain of the fibroblast growth factor receptor 3 (*FGFR 3*) gene in achondroplastic heterozygotes and homozygotes (3, 4). The achondroplasia mutation causes increased *FGFR3* activity disturbing both proliferation and hypertrophy of the epiphyseal growth plate chondrocytes as well as increasing the pace of osteogenesis (5, 6).

Growth hormone (GH) is an important factor for the growth and differentiation of chondrocytes. Trials with GH treatment in achondroplasia have been reported for a long time. Already in 1933, in Denmark, a treatment experiment was done using pituitary extracts in a patient with chondrodystrophy (presumably achondroplasia) (7). At the past nineties, there have been reports describing the beneficial effects of GH therapy in achondroplasia and hypochondroplasia (8-10), although

patients with achondroplasia are considered to have normal GH secretion. In fact, GH has been widely used to treat non-GH-deficient forms of short stature, such as Turner's syndrome, intrauterine growth retardation, chronic illness and idiopathic short stature (11-13). In the study of Bouali and Latrech (2015), a number of treatments for achondroplasia have been compared, including surgical limb lengthening and r-hGH treatment, to future treatments which include the natriuretic Peptide C-type (CNP) (14).

In the present study, we evaluated the effectiveness of GH administration on the enhancement of longitudinal bone growth in children with achondroplasia.

## 2. CASE REPORT

The patient T. M, 10 years old, was diagnosed with achondroplasia prenatally in the 7<sup>th</sup> month of gestation. His mother had a normal pregnancy, regularly controlled. The height of the mother is 163 cm, and of the father is 172 cm. The patient's only sibling is normal. Birth weight of the patient was 3150g, his length was 46 cm, with head circumference of 38 cm. He had all the stigmata of the skeletal dysplasia. He was referred to our endocrinology department for further follow-up after birth.

His psychomotor development was normal except for speech difficulties. Except the physical features of achondroplasia, he had a varus deformity of the knees. Ultrasound of the brain was performed on several occasions with normal findings. The Computerized Tomography (CT scan) of the brain did not reveal any abnormalities. His IgF1 levels (40mg/ml) and IgFBP3 levels (1900mg/ml) were normal. Two growth hormone stimulation tests were performed at the age of two years, and the values were within normal range. Thyrotropin releasing and thyroid hormone levels were also within normal range. The genetic testing revealed a mutation of C 1138 G>A in the gene *FGFR3* in a heterozygous constellation.

We started growth hormone treatment at the age of three years and four months in a dose of 0,06mg/kg.

## 3. RESULTS

At start his height was 82,3 cm and weight was 14 kg (Ht SDS -2, 2). Growth increased to 10cm/year in the first year of treatment (Ht SDS -1, 1). It decreased during the second year to four cm/year (Ht SDS -1, 7) and again increased during the third year to eight cm/year (Ht SDS -1, 3). In the next years the growth was constant (6, 5cm; 2, 3cm; 3,5cm /year). At the age of 10, he is still growing in the third percentile of the normal growth curve (Ht SDS -1, 2). The body disproportion did not aggravate during treatment.

## 4. DISCUSSION

r-hGH administration studies in achondroplasia have been limited, as it was thought initially that GH therapy would not be helpful, given that patients usually do not manifest a hormone deficiency. However, encouraging short-term results of GH treatment in achondroplasia have been reported. Although differing age groups, treatment periods, and dosages make comparison be-

tween studies difficult, it can be speculated that higher GH doses and younger age of initiation of treatment result in better growth response. Stamoyannou et al. (5) studied fifteen children with achondroplasia (seven boys 4. 8- 12. 2 years of age and twelve girls 5. 7- 12. 2 years of age). The patients were treated daily hGH at a dosage of 1 IU/kg/week. The authors of the study concluded that, hGH treatment resulted in an increased growth rate in some children with achondroplasia. However the increase waned during the second year of treatment, which was not the case in our study. Tanaka et al (1) treated forty two children (16 males and 26 females) with achondroplasia with GH for more than 2 years. GH was administered at a dose of 0.5 IU/kg/week or 1IU/kg/week for at least 2 years. The conclusion of this study was that GH might be beneficial in the treatment of short stature in children with achondroplasia in the first two years of treatment, in accordance to our study. Ramaswami et al (16) described the effects of GH therapy for up to 6 years on stature and body proportions of 35 children with achondroplasia. GH was administered at a median (range) dose of 30 (15. 8- 40) U/m<sup>2</sup> per week. Treatment caused a significant increase in Ht SDS year to year until year 4, that was subsequently sustained with no significant further change (year 5 and 6 versus year 4). Age, as in our study, was the most important variable accounting for the first-year response in Ht SDS and dose of r-hGH did not influence this. The conclusion was that a young age at initiation of therapy prevented the characteristic Ht deficit from accumulating. The greater increase in spinal Ht accentuated the existing disproportion. The addition of later surgical leg lengthening could offer the possibility of proportionate adult stature just within the normal range. Hertel et al (17) studied 35 achondroplastic children who received a dosage of either 0.1 IU/ kg/day or 0.2 IU /kg/day. GH treatment was interrupted for 12 months after 2 years of treatment in prepubertal patients to study catch-up growth. Mean growth velocity (baseline 4. 5/ 4. 6 cm/y for the groups) increased significantly by 1.9/ 3.6 cm/y during the first year and by 0.5/ 1.5 cm/y during the second year. These authors concluded that GH treatment in children with achondroplasia improves height during four years of therapy without adverse effect on trunk-leg disproportion, which data proved to be the same in our case.

The data from our case report demonstrated that GH treatment in a prepubertal achondroplastic child increased his growth by 10 cm/year in the first year of follow up. It decreased during the second year to four cm/year (Ht SDS -1. 7) and again increased during the third year to eight cm/year (Ht SDS -1.3). In the next years the growth was constant (6.5cm; 2.3 cm; 3.5 cm/year). At the age of 10, the treatment still continues, because he is growing in the third percentile of the normal growth curve (Ht SDS -1.2) and he has not yet reached his final height.

## 5. CONCLUSION

The growth was satisfactory in the first four years of treatment, although the patient still continued to grow.

His young age at start of the treatment was also of importance, which is the conclusion of other authors who performed similar studies. Also we had a longer period of favorable growth. Our other patients with achondroplasia who started treatment at an older age had a poor response to GH treatment.

- **Author's contribution:** Marina Krstevska-Konstantinova: substantial contribution to conception and design, final approval of the version to be published. Ana Stamatova: substantial contribution to conception and design, substantial contribution to acquisition of data, substantial contribution to analysis and interpretation of data, drafting the article. Zoran Gucev: substantial contribution to acquisition of data, substantial contribution to analysis and interpretation of data.
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### REFERENCES

1. Tanaka H, Kubo T, Yamate T. et al. Effect of growth hormone therapy in children with achondroplasia: Growth pattern, hypothalamic-pituitary function and genotype. *Eur J Endocrinol.* 1998; 138: 275-80.
2. Horton WA, Rotter JI, Rimoin DL et al. Standard growth curves for achondroplasia. *J Pediatr.* 1978; 93: 435-8.
3. Shiang R, Thompson LM, Zhu Y-Z et al. Mutations of the transmembrane domain of FGFR 3 causes the most common genetic form of dwarfism, achondroplasia. *Cell.* 1994; 78: 335-42.
4. Rousseau F, Bonaventure J, Legeai-Mallet L. et al. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. *Nature.* 1994; 371: 252-4.
5. Wang Q, Green RP, Zhao G. et al. Differential regulation of endochondral bone growth and joint development by FGFR1 and FGFR3 tyrosine kinase domains. *Development.* 2001; 128: 3867-76.
6. Ornitz DM, Marie PJ. FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev.* 2002; 16: 1446-65.
7. Mørch ET. Chondrodystrophic dwarfs in Denmark, Copenhagen: Munksgaard, 1941.
8. Nishi Y, Kajiyama M, Miyagawa S. et al. Growth hormone therapy in achondroplasia. *Acta endocrinologica.* 1993; 128: 394-6.
9. Horton WA, Hecht JT, Hood OJ. et al. Growth hormone therapy in achondroplasia. *American journal of Medical Genetics.* 1992; 42: 667-70.
10. Appan S, Laurent S, Chapman S. et al. Growth and growth hormone therapy in hypochondroplasia. *Acta Paediatrica Scandinavica.* 1990; 79: 796-803.
11. Hindmarsh PC, Bridges NA & Brook CGD. Wider indications for treatment with biosynthetic human growth hormone in children. *Clinical Endocrinology.* 1991; 34: 417-27.
12. Genentech Collaborative Study Group. Idiopathic short stature: results of a one-year controlled study of human growth hormone treatment. *Journal of Pediatrics.* 1989; 115: 713-9.
13. Chatelain P, Job JC, Blanchard J, Ducret JP. et al. Dose-dependent catch-up growth after 2 years of growth hormone treatment in intrauterine growth-retarded children. *Journal of Clinical Endocrinology and Metabolism.* 1994; 78: 1454-60.
14. Bouali H, Latrech H. et al. Achondroplasia: Current Options and Future Perspective. *Pediatr Endocrinol Rev.* 2015; 12(4): 388-95.
15. Stamoyannou L, Karachaliu F, Neou P. et al. Growth and growth hormone therapy in children with Achondroplasia: A two year experience. *American Journal of Medical Genetics.* 1997; 72: 71-6.
16. Ramaswami U, Rumsby G, Spoudeas HA. et al. Treatment of achondroplasia with growth hormone: six years of experience. *Pediatr Res.* 1999; 46(4): 435-9.
17. Hertel NT, Eklof O, Ivarsson S. et al. Growth hormone treatment in 35 prepubertal children with Achondroplasia: a five-year dose-response trial. *Acta Paediatr.* 2005; 94(10): 1402-10.