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# Effect of Growth Hormone treatment on Height Velocity of Children with Pycnodysotosis

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## Abstract

***Objective:*** Pycnodysostosis is a rare autosomal recessive osteochondrodysplasia resulting from osteoclast dysfunction. Growth hormone (GH) secretion impairment and low insulin growth factor 1 (IGF-I) concentrations have been reported in these patients. The present study aims to describe GH effect on linear growth of eight children with pycnodysostosis.

***Methods:*** This study was conducted on 8 children suffering from pycnodysostosis. After evaluating systemic diseases, adrenal insufficiency, and hypothyroidism, bone age, height standard deviation score (HtSDS), body mass index (BMI), and some demographical characteristics were measured. To measure the serum GH, we performed two clonidine tests in two different days with an interval of 24 hours. With initiation of the trial, human GH was injected subcutaneously once a day 6 days a week for a period of 1.5 years. The patients were followed up every 3 months to document their height and BMI until 6 months after the end of the treatment.

***Findings:*** All of the patients had growth hormone deficiency. HtSDS at the first visit continued to decrease during the 6 months before starting the treatment; however, HtSDS started to increase after beginning of GH administration. This value again declined after discontinuing the GH. Overall, the mean of linear growth was improved after GH administration in the patients.

***Conclusion:*** The present clinical study revealed that GH administration had a positive impact on the linear growth of the children suffering from pycnodysostosis.

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***Key Words:*** Pycnodysostosis; Growth Hormone Treatment; Linear Growth; Height

## Introduction

Pycnodysostosis is a rare autosomal recessive osteochondrodysplasia resulting from osteoclast dysfunction[1,2]. The disease symptoms include increased bone density, short stature, hypoplasia of the mandible, an obtuse mandibular angle, dysplasia of the skull bones with unossified fontanels and separated cranial sutures, partial aplasia of the terminal phalanges, stubby hands and feet with dystrophic nails, spondylolysis of the lumbar vertebrae, clavicular dysplasia, and increased tendency towards pathological fractures[3-7]. Growth hormone (GH) secretion impairment and low Insulin-like growth factor 1 (IGF-1) concentrations were also reported in these patients[3]. In many other syndromes such as Prader-Willi and skeletal dysplasia, there is defect in growth hormone and IGF-1 axis which hasn't been declared yet so as growth hormone deficiency in pycnodysotosis[8]. The prevalence of pycnodysostosis has been reported to be approximately 1.7 per million individuals with equal sex distribution. Less than 200 patients have been reported worldwide[9]. Mutations in the gene identified for coding of cathepsin K, a lysosomal

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cysteine protease localized exclusively in osteoclasts, were suggested to be responsible for this disease[10].

Considering the extremely short stature as well as other complications of these children in their adulthood and limited investigations on the treatment of this disorder, the present study aims to describe GH level and effect of this hormone on linear growth in eight children suffering from pycnodysostosis.

## Subjects and Methods

The present study was conducted on 8 children with clinical and radiological features of pycnodysostosis in the age range of 3-6 years at Endocrinology Clinic, Shiraz, southern Iran, from May 2010 to November 2012. Before any interventions, all parents of the patients filled the consent forms for participating in this study. In the first visit, children with clinical and radiological symptoms of pycnodysostosis were included in this study and then all systemic diseases, adrenal insufficiency, hypothyroidism, and also the compliance of the patient's family were evaluated and in case of any dissatisfaction in this appraisal, the patient was excluded from the study. Bone age was determined as well (by using left wrist radiography). Height standard deviation score (HtSDS), body mass index (BMI), and some other demographical characteristics of the patients were measured since 6 months prior to any treatment and continued during and after the end of the GH treatment. After obtaining a basal blood sample, a standard oral clonidine test (0.15 mg/m$^2$) was performed twice; in a way that serum samples were obtained every 30 minutes for two hours in order to measure the serum GH. With initiation of the trial, human GH was injected subcutaneously once a day 6 days a week for a period of 1.5 years (50μg/kg/day). The patients were followed up for 3 months in order to document their height and BMI until 6 months after the end of the treatment. Besides musculoskeletal examination (like for scoliosis), serum glucose, thyroid hormone and cortisol level were attained in these follow ups in order to assess complications of GH administration (every 6 months). IGF-1 was measured every 6 months after beginning the treatment which was in the normal range based on age and sex and there was no need to adjust GH.

The data are expressed as mean ± standard deviation. The charts are also expressed as mean±standard deviation in each point. All the statistical analyses were performed via SPSS® statistical software. One-way ANOVA test was used for comparison of the study group in different courses of treatment. Besides, *P*-value ≤0.05 was considered as statistically significant.

## Findings

Participants of this study were 8 children (4 girls and 4 boys) in the age range of 3-6 years. All of the subjects had GH deficiency and bone ages were lower than the chronological age. According to Table 1, the children's mean BMI at each visit had increased in comparison to the previous visit

**Table 1:** Patients' data before receiving growth hormone (GH) treatment, at first visit, and body mass index (BMI) before, during, and after receiving GH treatment

| Patient | sex | Age (year) | Bone age (year) | GH level (μg/l) | | BMI before GH treatment | | BMI during GH treatment | | | BMI 6 mo after discontinuing GH treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 0 mo | 6 mo | 6 mo | 12 mo | 18 mo | |
| 1 | f | 3.5 | 2 | 7.5 | 8 | 18.28 | 19.45 | 19.74 | 19.94 | 19.28 | 19.05 |
| 2 | m | 5.16 | 4.16 | 8.5 | 7 | 19.23 | 19.95 | 20.91 | 20.07 | 20.46 | 20.89 |
| 3 | f | 4 | 3 | 9 | 8 | 18.71 | 20.01 | 19.02 | 19.72 | 19.26 | 20.5 |
| 4 | m | 4.25 | 3.66 | 7.3 | 8.5 | 20.19 | 20.43 | 21.83 | 22.17 | 22.27 | 21.7 |
| 5 | f | 5.5 | 4.16 | 6.5 | 9 | 16.27 | 17.18 | 17.82 | 19.13 | 18.51 | 19.29 |
| 6 | m | 4.33 | 3 | 8.6 | 7.3 | 17.24 | 18.69 | 19.18 | 20.4 | 20.26 | 20.86 |
| 7 | f | 5.91 | 3.5 | 5 | 6.9 | 15.37 | 16.77 | 17.19 | 17.45 | 18.33 | 18.17 |
| 8 | m | 5.66 | 4 | 8.8 | 6.5 | 16.33 | 17.3 | 18.14 | 19.29 | 20.06 | 19.97 |
| Mean (SD) | - | 4.79 (0.88) | 3.43 (0.74) | 7.65 (1.37) | 7.65 (0.86) | 17.70 (1.66) | 18.72 (1.45) | 19.22 (1.56) | 19.77 (1.32) | 19.80 (1.26) | 20.05 (1.16) |

**Table 2:** Descriptive data of Patients' Height SD score before, during, and after discontinuing GH treatment

| Patient | HtSDS before GH treatment | | | HtSDS during GH treatment | | | | | HtSDS after discontinuing treatment | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1st visit | 3 mo | 6 mo | 3 mo | 6 mo | 9 mo | 12 mo | 15 mo | 18 mo | 3 mo | 6 mo |
| 1 | -5.45 | -5.53 | -5.63 | -5.55 | -5.50 | -5.50 | -5.31 | -5.01 | -4.96 | -4.98 | -5.01 |
| 2 | -4.04 | -4.34 | -4.62 | -4.50 | -4.37 | -4.28 | -4.25 | -4.01 | -3.76 | -3.91 | -4.04 |
| 3 | -4.57 | -4.60 | -4.92 | -4.62 | -4.57 | -4.51 | -4.31 | -4.22 | -4.15 | -4.16 | -4.28 |
| 4 | -4.19 | -4.50 | -4.85 | -4.71 | -4.25 | -3.99 | -3.95 | -3.87 | -3.69 | -3.89 | -4.23 |
| 5 | -4.05 | -4.11 | -4.15 | -4.11 | -4.07 | -3.99 | -3.88 | -3.69 | -3.62 | -3.73 | -3.87 |
| 6 | -4.13 | -4.47 | -4.62 | -4.58 | -4.53 | -4.48 | -4.30 | -4.11 | -3.95 | -3.98 | -4 |
| 7 | -3.15 | -3.26 | -3.65 | -3.50 | -3.20 | -3.13 | -3.03 | -3.06 | -3.02 | -3.20 | -3.24 |
| 8 | -3.32 | -3.41 | -3.59 | -3.51 | -3.48 | -3.40 | -3.37 | -3.40 | -3.36 | -3.41 | -3.44 |
| Mean | -4.11 | -4.27 | -4.50 | -4.38 | -4.24 | -4.16 | -4.05 | -3.92 | -3.81 | -3.91 | -4.01 |
| (SD) | (0.71) | (0.71) | (0.68) | (0.67) | (0.71) | (0.73) | (0.69) | (0.58) | (0.58) | (0.53) | (0.54) |

SD: Standard Deviation; HtSDS; Height SD score; GH: growth hormone

during GH therapy and in most of the cases it was decreased in the follow ups after discontinuing GH. In addition, Table 2 shows that all the patients had a HtSDS below -3.5 at the first visit which continued to decrease during the 6 months before starting the treatment; however, HtSDS started to increase after beginning of GH administration. This value again declined after discontinuing the GH therapy. This fluctuation is shown in Fig. 1. The mean value of growth was improved after GH therapy in the patients, in both males and females separately (Fig. 2).

It was demonstrated that height velocity of patients during GH therapy was significantly different in comparison to growth rate before and after this time period.

## *Discussion*

Pycnodysostosis is an inherited disorder of the bone remodeling and dwarfism is one of its major features[11]. This presentation is due to some reasons, such as involvement of vertebrae, chronic airway obstruction, hypoxemia, marked anemia, chromosomal anomalies associated with the disease, and malnutrition secondary to dental disorders[3]. So far, no specific treatment has been validated in pycnodysostosis except for symptomatic therapy[9,12].

Up to now only a few studies have been conducted on growth hormone level and effect of growth hormone therapy on linear growth in the children with pycnodysostosis. The prevalence of

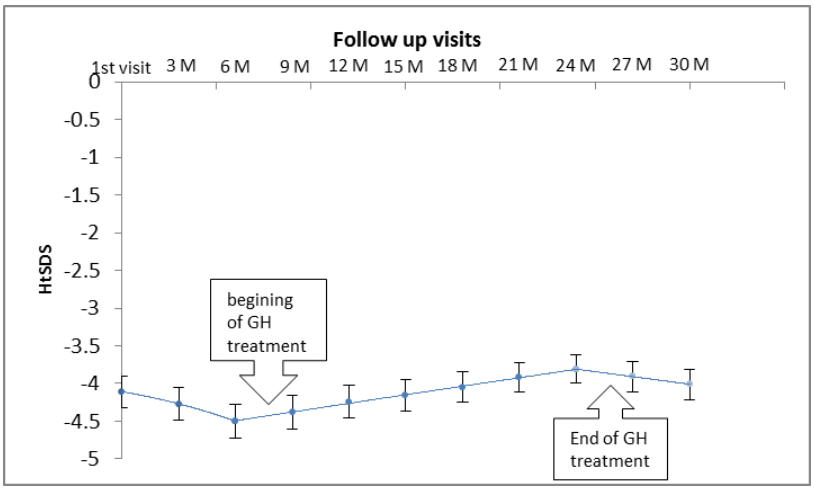


**Fig. 1:** Curved line: Mean (SD) of the values in each visit; HtSDS starts to increase after beginning of growth hormone (GH) treatment and decreases again after stopping GH administration

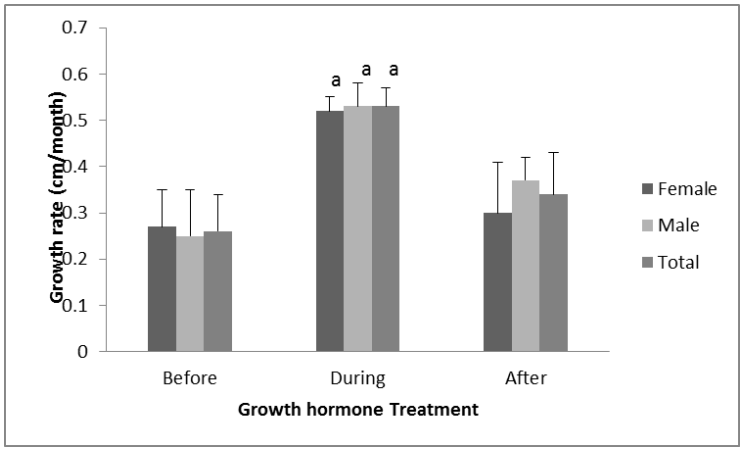


**Fig. 2:** Mean (±SD) of Growth rates (cm/month) in patients suffering from Pycnodysostosis. "a" indicates significant difference between the growth rate during growth hormone treatment versus before and after the treatment ($P$<0.001).

growth hormone deficiency in pycnodysostosis is still unknown. In the present study which was conducted on 8 children suffering from this disease, all patients had growth hormone deficiency after 2 provocative growth hormone assay tests. In a case report, Darcan et al described a patient with pycnodysostosis and growth hormone deficiency in whom the growth rate improved after growth hormone treatment[13]. Rothenbuhler et al demonstrated that GH therapy developed growth noticeably in the children with pycnodysostosis, reaching midparental height instead of the short 140±10 cm height in adulthood resulting from the disease[14]. In a study performed by Soliman et al (1996), defective GH secretion associated with hypoplasia of the pituitary gland was detected in 4 of the 8 children with pycnodysostosis[15] which was explained later by increased intrasellar pressure due to the increased bone volume and leading to the pituitary hypoplasia and partial GH deficiency in some of these patients[16]. Soliman et al (2001) also showed that a lot of patients suffering from pycnodysostosis had GH secretion impairment and low IGF-I concentrations. Besides, they reported a dramatically increased IGF-I secretion and improvement of linear growth after GH therapy[3].

The present clinical study revealed that GH administration had a positive impact on the linear growth of the children suffering from pycnodysostosis, which could be due to defective GH secretion and low IGF-I concentrations in the setting of this disease. However, there are a few studies on pycnodysostosis which make this disease still a concern for researchers and clinicians.

Still, there is no effective therapy for this disorder. Therefore, proposing agents affecting the final height of these patients could affect their future life and this study could be a step forward in this scenario; nevertheless, other dosages, the exact needed period of therapy, and also complications are not investigated in this work; therefore, this emphasizes the importance of continuance of this thesis via future studies.

## Conclusion

Outcome of the present study implies that GH treatment is beneficial for linear growth of patients suffering from pycnodysostosis, particularly since they showed GH deficiency; however, the effect of this hormone on the final height of the patients is not apparent and more researches are needed to determine all aspects and also complications of long term hormone therapy in these patients and prevent the progression of skeletal abnormalities and correct the abnormal bone metabolism in these cases. As this disease is so rare and all the children with pycnodysostosis participating in this study were suffering from growth hormone deficiency, it was impossible to investigate the effect of this agent in the patients with pycnodysotosis without GH deficiency. Scarcity of the cases was also another

limitation for this study and finding this amount of the patients was so unlikely.

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### *Authors' Contribution*

Z. Karamizadeh: Concept, Data interpretation, Study supervision
H. Ilkhanipoor: Acquisition of data, Data analysis, Drafting of the manuscript
F. Bagheri: Data analysis, Draft of manuscript
All authors approved final version of the paper.

***Conflict of Interest:*** None

## *References*

1. Naeem M, Sheikh S, Ahmad W. A mutation in CTSK gene in an autosomal recessive pycnodysostosis family of Pakistani origin. *BMC Med Genet* 2009;10: 76-80.
2. Fleming KW, Barest G, Sakai O. Dental and facial bone abnormalities in pyknodysostosis: CT findings. *AJNR Am J Neuroradiol* 2007;28(1):132-4.
3. Soliman AT, Ramadan MA, Sherif A, et al. Pycnodysostosis: clinical, radiologic, and endocrine evaluation and linear growth after growth hormone therapy. *Metabolism* 2001;50(8):905-11.
4. Zenke MS, Hatori M, Tago S, et al. Pycnodysostosis associated with spondylolysis. *Arch Orthop Trauma Surg* 2002;122(4):248-50.
5. Karakurt L, Yilmaz E, Belhan O, et al. Pycnodysostosis associated with bilateral congenital pseudarthrosis of the clavicle. *Arch Orthop Trauma Surg* 2003;123(2-3):125-7.
6. Osimani S, Husson I, Passemard S, et al. Craniosynostosis: A rare complication of pycnodysostosis. *Eur J Med Genet* 2010;53(2):89-92.
7. Li HY, Ma HW, Wang HQ, et al. Molecular analysis of a novel cathepsin K gene mutation in a Chinese child with pycnodysostosis. *J Int Med Res* 2009;37(1): 264-9.
8. Gottschling S, Graf N, Meyer S. Intracranial germinoma: a rare but important differential diagnosis in children with growth retardation. *Acta Paediatr* 2006; 95(3):302-5.
9. Mujawar Q, Naganoor R, Patil H, et al. Pycnodysostosis with unusual findings: a case report. *Cases J* 2009; 2:6544.
10. Fujita Y, Nakata K, Yasui N, et al. Novel mutations of the cathepsin K gene in patients with pycnodysostosis and their characterization. *J Clin Endocrinol Metab* 2000;85(1):425-31.
11. Chavassieux P, Seeman E, Delmas PD. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease. *Endocr Rev* 2007; 28(2):151-64.
12. Chavassieux P, Karsdal MA, Segovia-Silvestre T, et al. Mechanisms of the anabolic effects of teriparatide on bone: insight from the treatment of a patient with pycnodysostosis. *J Bone Miner Res* 2008;23(7): 1076-83.
13. Darcan S, Akisu M, Taneli B, et al. A case of pycnodysostosis with growth hormone deficiency. *Clin Genet* 1996;50(5):422-5.
14. Rothenbühler A, Piquard C, Gueorguieva I, et al. Near normalization of adult height and body proportions by growth hormone in pycnodysostosis. *J Clin Endocrinol Metab* 2010;95(6):2827-31.
15. Soliman AT, Rajab A, AlSalmi I, et al. Defective growth hormone secretion in children with pycnodysostosis and improved linear growth after growth hormone treatment. *Arch Dis Child* 1996; 75(3):242-4.
16. Gowen M, Lazner F, Dodds R, et al. Cathepsin K knockout mice develop osteopetrosis due to a deficit in matrix degradation but not demineralization. *J Bone Miner Res* 1999;14(10):1654-63.