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Case Report

Recombinant GH treatment in a case of Costello syndrome with a 5-year follow-up

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Abstract. Costello syndrome (CS) is a rare member of the group of neuro-cardio-facio-cutaneous diseases known as RASopathies. CS involves characteristic dysmorphic craniofacial features, cardiac defects, and increased cancer susceptibility, depending on the heterozygous activating germline mutations in *HRAS*. Polyhydramnios and high birth weight are the most common presentations in the perinatal and neonatal periods; while poor postnatal growth, short stature, and failure to thrive are significant issues in infancy. Possible mechanisms of short stature in CS include GH deficiency and feeding difficulties. Only a few reported cases of CS with GH deficiency exist in literature. Here, we describe the 5-yr follow-up of a CS patient with complete GH deficiency treated with recombinant human GH (rhGH) from the age of four years. No significant adverse events regarding progression of hypertrophic cardiomyopathy and tumor development were observed. She has been responsive to treatment with improved growth velocity and height standard deviation scores. She is still under continuous monitoring for concerns on the possible development of cardiac events and malignancies. This case indicated that rhGH therapy is effective for improving the height and growth velocity of CS patients with GH deficiency under close cardiac and oncological monitoring.

Key words: Costello syndrome, GH deficiency, *HRAS*, malignancy

Introduction

Costello syndrome (CS, OMIM 218040) is one of the uncommon RASopathies, characterized by typical fascial dysmorphism, heart defects, severe short stature, feeding difficulties, developmental delays, failure to thrive, and increased risk of tumorigenesis. The syndrome was first described by Dr. J. M. Costello in two children with identical fascial appearance, poor postnatal growth, mental subnormality, and nasal papilloma in 1971–1977 (1). The growth failure in CS was defined in the 1990s (2). As described in the 2000s, the syndrome is caused by a heterozygous activating germline mutation in *HRAS*, located on 11p15.5 (3).

Polyhydramnios, macrocephaly/relative macrocephaly, cardiac defects, and arrhythmia, are common prenatal signs of CS, as they are of Noonan syndrome and cardio-facio-cutaneous syndrome. Today, Sanger sequencing is the gold standard method for molecular diagnosis of RASopathies. Prenatal molecular diagnosis of CS is possible by ruling out the absence of *HRAS* mutations (4).

GH deficiency is described in 30–50% of CS patients (5). CS also have a predisposition towards malignancies (6). Since both CS and recombinant human GH (rhGH) treatment can increase the risk of developing malignancies and cardiomyopathies, rhGH treatment for CS patients is an important matter of debate. There is currently no patient-derived outcome data on the benefits or disadvantages of GH replacement. Multidisciplinary monitoring of patients during both the pretreatment and treatment periods should therefore be performed (5).

We hereby report a patient with complete growth hormone deficiency who received rhGH treatment for five years with no significant adverse events. This case indicated that GH therapy is effective for improving height and growth velocity.

Case Report

A four-year-old female patient was admitted to our outpatient clinic due to short stature. She was born to non-consanguineous parents via elective

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cesarean section at 38 wk of gestation following an uncomplicated pregnancy, with a birth weight of 3,390 g. In early infancy, she suffered from feeding difficulties, hypotonia, gastrointestinal reflux, and failure to thrive with no history of hypoglycemia. A gastrostomy tube was required for feeding. At 10 mo of age, a molecular test was performed due to developmental delay and dysmorphic facial features such as epicanthal folds, a short nose with a flat-depressed nasal bridge and anteverted nares, and posteriorly rotated low-set ears with large lobes. A whole exome sequence analysis was performed at the Center for Human Genetics (Centrum Menselijke Erfelijkheid, CME) at the Gasthuisberg campus of UZ Leuven in Belgium. A heterozygous mutation, c.34G> A (p.Gly12Ser), in exon 2 of the *HRAS* gene was revealed, which is the most common mutation responsible for CS. A definitive diagnosis of CS was hence achieved.

At first evaluation at 4.2 yr of age, the patient's height was 88.7 cm (–3.49 SD) and her weight was 12.38 kg (–2.29 SD). The mid-parental height was 164 cm, corresponding to 0.15 SD (her mother's height was 159 cm, and her father was 182 cm). On physical examination, characteristic phenotypic features of CS were noted: coarse face, prominent forehead, epicanthal folds, down-slanting palpebral fissures, curly hair, broad and short nose, posteriorly rotated ears with thickened lobes and helices, full cheeks, high arched palate, full lips with large mouth, short neck, as well as dark, loose and soft skinned hands and feet with wrinkling-hypoplastic nails. A gastrostomy scar was noticed. Laboratory tests showed normal hemogram and biochemical parameters, including liver and kidney function, blood glucose, thyroid function, tissue transglutaminase autoantibody Ig A, and serum total Ig A level. Her urine analysis was normal. GH stimulation tests with L-dopa and glucagon revealed low basal GH levels and reduced GH response (peak GH of 1.51 ng/ml and 0.95 ng/ml, respectively) with low IGF1 levels (11.3 ng/ml, –2.39 SD). Her bone age was 2 yr and 6 mo. Magnetic resonance imaging of the cranium and hypophysis was normal. These findings were compatible with GH deficiency. Long term risks and benefits of medical treatment were discussed with the parents, and initiation of medical treatment was decided upon.

rhGH treatment was initiated at 0.2 mg/kg/wk, which was the standard dose at the age of 4.2 yr. The patient responded with significantly improved linear growth, growing 9.5 cm/yr in the first year of treatment. She continued to grow at 6.8 cm/yr, 6 cm/yr, and 7 cm/yr in the next three years, respectively. In the fifth year of the treatment, her growth velocity slowed down to 5.52 cm/yr, and rhGH treatment was increased to 0.23 mg/kg/wk at the age of 9.58 yr. Bone age was 8 yr and 10 mo. Onset of left breast development was realized at 9.58 yr old with no signs of pubarche (**Table 1**).

The patient was followed-up every three months of treatment for evaluation of growth velocity, response to the treatment, and side effects. Her bone age progression was evaluated annually. Her IGF-1 levels were maintained in the normal range for the age, gender, and pubertal stage. No pathological laboratory results were obtained. Due to concerns of potential cardiac and neoplastic effects of CS, regular monitoring with electrocardiogram, echocardiography, and abdominal and pelvic ultrasonography was done. The plasma concentrations of metanephrine and normetanephrine were assessed every 3–6 mo. No pathological ultrasonographic findings were observed. The repeated echocardiogram was normal with no evidence of hypertrophic cardiomyopathy. At the age of 9.5 yr, mild tricuspid and mitral regurgitation with normal cardiac function were documented (**Table 1**).

Over five years of rhGH treatment, no adverse effects have been observed. While total height gain was 36.3 cm; total change in height SD (ΔHSD) was +1.86 at the end of the five-year treatment course, with

Table 1. Follow-up charachteristics of the patient

Age (yr)	Height (cm)	Height SD	Δ Height SD	Growth velocity (cm/yr)	Weight (kg)	BMI (kg/m^2)	BMI percentile (%)	GH (mg/kg/wk)	Bone age	Puberty stage	USG /ECHO	Plasma metanephrine normetanephrine level
4.24	88.7	–3.49	–	–	12.38	15.74	102.07	0.2	2 yr 6 mo	T1P1	Abdominal USG: N ECHO: N	–
5.35	98.2	–2.47	1.02	9.5	13	13.48	86.51	0.2	3 yr	T1P1	Abdominal USG: N ECHO: N	N
6.42	105	–2.16	0.31	6.8	18.1	16.42	88	0.2	5 yr	T1P1	Abdominal USG: N ECHO: N	N
7.4	111	–2.07	0.09	6	17.15	13.92	89	0.2	6 yr 10 mo	T1P1	Abdominal USG: N ECHO: N	N
8.49	119	–1.62	0.45	7	20.2	14.26	85.3	0.2	7 yr 10 mo	T1P1	Abdominal USG: N ECHO: TR (mild) MR (mild)	N
9.58	125	–1.63	0	5.52	22.7	14.53	92.9	0.23	8 yr 10 mo	T1T2P1	Abdominal USG: N ECHO: TR (mild) MR (mild)	N

USG, ultrasonography; ECHO, echocardiogram; TR, tricuspid regurgitation; MR, mitral regurgitation; N. normal; BMI, body mass index; Δ Height, delta Height.

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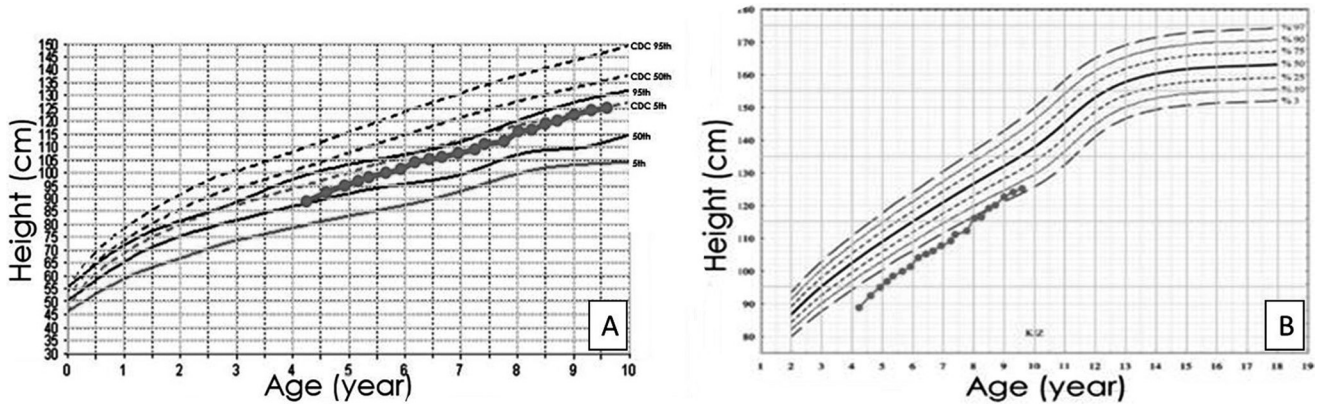

Fig. 1. (A) Growth curves of the patient according to normative growth charts for individuals with Costello syndrome (23). (B) Growth curves of the patient according to national growth charts for healthy children (24).

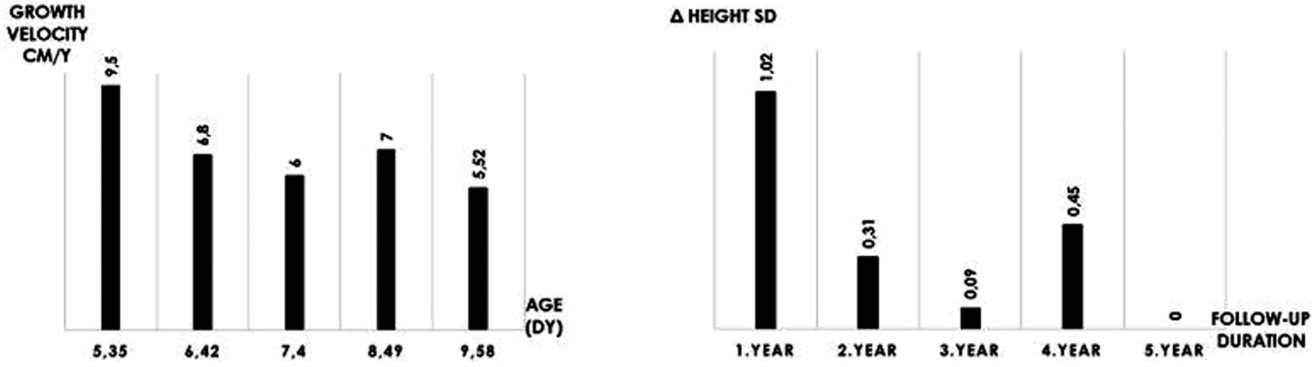

Fig. 2. Growth velocity and delta (Δ) height SD of patient.

significantly increased linear growth of +1.02 ΔHSD during the first year of rhGH therapy, and +0.31 ΔHSD, +0.09 ΔHSD, +0.45 ΔHSD, and –0.01 ΔHSD in the next four years, respectively. Her current height has reached above the 3rd percentile. In growth monitoring, height and weight of the patient are plotted on charts for both CS and healthy national children (**Figs. 1 and 2**). She is still on daily rhGH injections. She has attended kindergarten and primary school and receives moderate grades.

Informed consent was obtained from all individuals included in this case presentation.

Discussion

RASopathies are a group of neuro-cardio-fascio-cutaneous diseases occurring secondary to germline mutation in the RAS/mitogen-activated protein kinase (MAPK) pathway. This pathway plays a significant role in the cell cycle, including cell development, differentiation, migration, and survival. Dysregulation of the MAPK pathway is, not surprisingly, one of the most common causes of cancers. Mutations in *RAS* genes, such as *HRAS*, *NRAS*, and *KRAS*, account for 20% of malignancies; therefore, RASopathies are well-known cancer syndromes. The genomic phenomic interactions have been well-described in many studies. As a group, the prevalence of RASopathy syndromes is almost 1 in 1,000 (7, 8)

CS, an uncommon form of RASopathy with a prevalence of 1/300,000, is caused by heterozygous activating mutations in *HRAS* in at least 85% of cases. The most common substitution is p.Gly12Ser (71%), which was observed in our patient; followed by p.Gly12Ala (9%) and p.Gly13Cys (6%). Although the malignancy risk of CS with a G12A mutation has been elucidated, all studies emphasized that genotype-phenotype correlation research of larger sample size is needed. P.Gly12Ser is not directly associated with an increased risk of malignancy, although there are some reports of rhabdomyosarcoma during the follow-up of patients with a p.Gly12Ser mutation (5, 9–12).

CS has certain distinctive features throughout the life period. Prenatal features are nondistinctive, but polyhydramnios (> 90%) is the most common ultrasound finding during the perinatal period. However, polyhydramnios was not observed in the fetal period of our patient. Newborns with CS are typically overweight. The most significant problem of most infants with CS is the failure to thrive. Feeding difficulty, hypotonia, gastroesophageal reflux, and poor suck reflex have been reported. In some cases, as in our case, a gastrostomy tube was needed (5, 7, 12).

Short stature may be caused not only by feeding

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difficulties during infancy, but also by partial or complete GH deficiency, which is seen in as high as 30–50% of CS patients (12). Since CS is a predisposing cancer syndrome, appropriate screening protocols should be followed. Benign tumors such as papilloma in the perioral, perinasal, and/or perianal regions, are frequent in childhood. Premalignant and malignant neoplasms are the greatest concerns. Rhabdomyosarcoma (RMS), predominantly embryonal, is the most frequent cancer seen in reported cases. Neuroblastoma and transitional cell carcinoma of the bladder are other types of CS-associated malignancies. Although transitional cell carcinoma of the bladder is typically seen in adults, it can also occur in individuals with CS during childhood (13). Our patient showed typical characteristic features of CS, such as a coarse facial appearance, which include a prominent forehead, thick eyebrows, down-slanting palpebral fissures, epicanthal folds, full cheeks, a short nose with flat-depressed nasal bridge with anteverted nares, posteriorly rotated low-set ears with large lobes, a large mouth with full lips, macroglossia, a short neck, fine curly hair, as well as loose, soft skin with deep palmar and plantar creases. However, she showed no signs of either cardiovascular disease or tumor development. The reported incidence of cancer appears to be approximately 17% of CS cases (14). Decision for the use of rhGH in CS patients is difficult because rhGH further increases the risk of cancer. However, our patient showed severe short stature (–3.49 SD). According to reported cases, the average adult height of individuals with CS is 138 cm (between 118 to 148 cm) (15). If rhGH treatment were to be decided upon, the patient should be screened by echocardiography and abdominal ultrasound. The risks and benefits should be weighed individually in all patients considering GH therapy (16). Although there are only a few published case reports on the long term outcomes of rhGH treatment in CS, and its effectiveness has been largely debatable, we provided the treatment with close and careful monitoring.

Since GH plays a key role in mitogenesis, anti-apoptosis, and proangiogenesis, there has always been a concern about the use of rhGH therapy in tumor-predisposing syndromes. the increase in serum levels of IGF-1 reflects a higher possibility of cancer development (17). In the literature about rhGH treatment of CS, patients with total GH deficiency responded successfully to rhGH without the development of tumors and cardiac abnormalities (18–21), whereas those with partial GH deficiency and accompanying endocrinological problems such as hypoglycemia and cortisol deficiency, responded poorly to rhGH therapy (22). Two issues should be considered during the follow-up of rhGH treatment: cardiac hypertrophy and the risk of malignancy development. The National Co-operative Growth Study revealed that cardiac side effects in children on rhGH were rare. A case report involving two CS patients who developed cardiomyopathy on rhGH suggested considering the benefits both with and without rhGH. We have closely monitored our patient, and no serious side effects related to rhGH treatment and CS were detected. During the first year of treatment, ΔHSD increased by +1.02 SD which indicated a good response to rhGH. Her current height is 125 cm (SD: –1.63) with total ΔHSD of +1.86 observed at the end of the five years of treatment. Response to GH therapy has been highly variable in the literature; however, in terms of individualization of GH therapy for the optimal response, our patients represented a good example.

In the case report assessing two CS cases on rhGH therapy, rhGH discontinuation was initially planned in the first case due to the development of hypertrophic cardiomyopathy in the third month of treatment. However, the family insisted on following-up treatment without interruption, and no worsening of cardiomyopathy was observed. In the second case, although serum IGF-1 level was below –2SD, RMS was observed in the 26th mo of treatment. rhGH therapy was immediately stopped. Despite chemotherapy, the patient died. This case report showed that development of malignancy in CS should not be directly linked to the use of rhGH (16).

Based on the newest guidelines for CS, abdominal and pelvic ultrasound should be repeated every three months until age 8–10 yr. Annual urinalysis screening should be done from age 10 to exclude the potential development of tumors. To screen for cardiac comorbidities, ECG and echo assessments are recommended every six months under age 2, and every 2–3 yr between ages 2 and 20 yr. Fasting lipid levels should be tested between ages 9–11. Individuals diagnosed with CS should immediately be indicated for nutritional evaluation, growth assessment, and early diagnosis of endocrinological comorbidities, including hypoglycemia, delayed or precocious puberty, GH deficiency, and hypothyroidism (5). No additional endocrinological problems were detected in our patient, except for GH deficiency.

In our patient, no adverse events were observed during her five-year rhGH treatment period, and she responded well to treatment. Both the normative growth charts for CS and the national growth charts for healthy children were used because of limitations in the CS-specific curves towing to the rarity of CS (23). Our patient fell within the 50th and 95th percentile of the growth curves for CS, and caught up to the normal growth curve for age and gender with normal growth velocity (5.5 cm/yr) (24).

During her follow-ups, IGF-1 levels have been below +2 SD. The p.Gly12Ser mutation observed in our patient does not directly link to tumor growth. Before starting rhGH treatment, our patient underwent cardiological evaluation with echocardiography. In the fifth year of therapy, mild tricuspid and mitral regurgitation with normal cardiac function were observed, which was thought to be a consequence of CS, not rhGH. In contrast with other CS cases reported, no development of cancer has been observed. However, she has been closely monitored as indicated in the newest guidelines for CS treatment.

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Conclusion

In our case of CS, a good response with improved growth has been demonstrated after a standard dose of rhGH. Concerns that rhGH may lead to the development of hypertrophic cardiomyopathy and malignancies associated with CS have not been validated in the five-year follow-up. Due to the limited number of studies on rhGH treatment for CS, research involving follow-ups on subjects' final height is warranted to provide precious data regarding the optimum treatment regimens for the improvement of growth in these children. Based on current guidelines, our patient is still on close cardiac and oncological monitoring.

Conflict of Interest: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication. No conflict of interest was declared by the authors.

References

1. Costello JM. A new syndrome: mental subnormality and nasal papillomata. Aust Paediatr J 1977;13: 114–8. [Medline]
2. Schimke R, Donaldson D, Moore W., editors. Growth hormone deficiency in Costello syndrome. Proc Greenwood Genet Ctr; 1996.
3. Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, *et al*. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet 2005;37: 1038–40. [Medline] [CrossRef]
4. Mucciolo M, Dello Russo C, D'Emidio L, Mesoraca A, Giorlandino C. Next generation sequencing approach in a prenatal case of cardio-facio-Cutaneus syndrome. Int J Mol Sci 2016;17: 952. [Medline] [CrossRef]
5. Gripp KW, Morse LA, Axelrad M, Chatfield KC, Chidekel A, Dobyns W, *et al*. Costello syndrome: Clinical phenotype, genotype, and management guidelines. Am J Med Genet A 2019;179: 1725–44. [Medline] [CrossRef]
6. Hennekam RC., editor. Costello syndrome: an overview. Am J Med Genet Part C: Seminars in Medical Genetics; 2003: Wiley Online Library.
7. Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet 2013;14: 355–69. [Medline] [CrossRef]
8. Pevec U, Rozman N, Gorsek B, Kunej T. RASopathies: presentation at the genome, interactome, and phenome levels. Mol Syndromol 2016;7: 72–9. [Medline] [CrossRef]
9. Kerr B, Delrue MA, Sigaudy S, Perveen R, Marche M, Burgelin I, *et al*. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. J Med Genet 2006;43: 401–5. [Medline] [CrossRef]
10. Bertola D, Buscarilli M, Stabley DL, Baker L, Doyle D, Bartholomew DW, *et al*. Phenotypic spectrum of Costello syndrome individuals harboring the rare HRAS mutation p.Gly13Asp. Am J Med Genet A 2017;173: 1309–18. [Medline] [CrossRef]
11. Choi N, Ko JM, Shin SH, Kim EK, Kim HS, Song MK, *et al*. Phenotypic and genetic characteristics of five Korean patients with Costello syndrome. Cytogenet Genome Res 2019;158: 184–91. [Medline] [CrossRef]
12. Gripp KW, Rauen KA. Costello syndrome. GeneReviews®[Internet]: University of Washington, Seattle; 2019.
13. Gripp KW., editor. Tumor predisposition in Costello syndrome. Am J Med Genet Part C: Seminars in Medical Genetics; 2005: Wiley Online Library.
14. Gripp KW, Scott CI Jr, Nicholson L, McDonald-McGinn DM, Ozeran JD, Jones MC, *et al*. Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol. Am J Med Genet 2002;108: 80–7. [Medline] [CrossRef]
15. van Eeghen AM, van Gelderen I, Hennekam RC. Costello syndrome: report and review. Am J Med Genet 1999;82: 187–93. [Medline] [CrossRef]
16. Kerr B, Einaudi M, Clayton P, Gladman G, Eden T, Saunier P, *et al.* Is growth hormone treatment beneficial or harmful in Costello syndrome? J MED GENET 2003;40(6):e74-e.
17. Burgers AMG, Biermasz NR, Schoones JW, Pereira AM, Renehan AG, Zwahlen M, *et al*. Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-I) and mortality. J Clin Endocrinol Metab 2011;96: 2912–20. [Medline] [CrossRef]
18. Blachowska E, Petriczko E, Horodnicka-Józwa A, Skórka A, Pelc M, Krajewska-Walasek M, *et al*. Recombinant growth hormone therapy in a girl with Costello syndrome: a 4-year observation. Ital J Pediatr 2016;42: 10. [Medline] [CrossRef]
19. Stein RI, Legault L, Daneman D, Weksberg R, Hamilton J. Growth hormone deficiency in Costello syndrome. Am J Med Genet A 2004;129A: 166–70. [Medline] [CrossRef]
20. Legault L, Gagnon C, Lapointe N. Growth hormone deficiency in Costello syndrome: a possible explanation for the short stature. J Pediatr 2001;138: 151–2. [Medline] [CrossRef]
21. Triantafyllou P, Christoforidis A, Vargiami E, Zafeiriou DI. Growth hormone replacement therapy in Costello syndrome. Growth Horm IGF Res 2014;24: 271–5. [Medline] [CrossRef]
22. Gregersen N, Viljoen D. Costello syndrome with growth hormone deficiency and hypoglycemia: a new report and review of the endocrine associations. Am J Med Genet A 2004;129A: 171–5. [Medline] [CrossRef]
23. Sammon MR, Doyle D, Hopkins E, Sol-Church K, Stabley DL, McGready J, *et al*. Normative growth charts for individuals with Costello syndrome. Am J Med Genet A 2012;158A: 2692–9. [Medline] [CrossRef]
24. Neyzi O, Gunoz H, Furman A, Bundak R, Gokcay G, Darendeliler F, *et al*. Weight, height, head circumference and body mass index references for Turkish children. Cocuk Sagligi ve Hastalikari Dergisi 2008;51: 1–14.

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