PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2013) **55**, e162–e164 doi: 10.1111/ped.12215

Patient Report

Treatment of cartilage–hair hypoplasia with recombinant human growth hormone

Monika Obara-Moszynska,[1] Weronika Wielanowska,[1] Aleksandra Rojek,[1] Danuta Wolnik-Brzozowska[2] and Marek Niedziela[1]

Departments of [1]Pediatric Endocrinology and Rheumatology and [2]Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland

Abstract Cartilage–hair hypoplasia (CHH) is an autosomal recessive disorder characterized by short stature, hypoplastic hair and humoral immunity disorders. It is a mutation in the *RMRP* gene, located on chromosome 9p13.3, that leads to CHH. There is no special treatment for short stature in CHH. The efficacy and safety of recombinant human growth hormone (rhGH) therapy in CHH is still under discussion. The present study describes the case of a girl with CHH who was treated with rhGH. The rhGH treatment had a significant effect on the height gain: the height SD score was changed from –4. to –2.98 after 4 years 7 months of treatment. rhGH therapy should be considered as a treatment modality for CHH, and insulin-like growth factor (IGF)-1 and IGF-binding protein 3 concentrations should be closely monitored, particularly because of the increased cancer risk that is a characteristic feature of CHH.

Key words bone disease, cartilage–hair hypoplasia, chondrodysplasia, growth hormone, short stature.

Cartilage–hair hypoplasia (CHH; OMIM ID: 250250), also known as the McKusick type of metaphyseal chondrodysplasia, is a rare autosomal recessive disorder caused by a mutation in the ribonuclease of mitochondrial RNA-processing complex (*RMRP*) gene (OMIM ID: *157660), located on chromosome 9p13.3.[1] This gene is required for cellular growth, which explains why its mutation affects cartilage development (subsequently inducing bone dysplasia), as well as humoral immunity (mostly T cells). Unlike many genes, the *RMRP* gene does not encode for a protein for the RNA component of a mitochondrial RNA-processing endoribonuclease, namely RNase MRP.[2] RMRP instead relates to a large complex involved in the replication of mitochondrial DNA, biogenesis of 5.8S rRNA and the cleavage of cyclin B2 mRNA, crucial for cell cycle control.[3]

Defective RNase MRP complex results in short stature (dwarfism), bone abnormalities, immune deficiency, an increased risk of developing cancer (primarily lymphomas and skin carcinoma), fine, sparse and light hair (hypotrichosis), and other signs and symptoms characteristic of CHH such as disproportionate shortening of the limbs and bowing of the legs.[4] The patients are also prone to scoliosis, Hirschsprung's disease, anemia as well as recurrent infections.[5–7] The disease is visible at birth, with evident shortening of the limbs, but may be detected *in utero* by observations of the fetal femur (its length and bowing).

The therapy in CHH is focused on immunodeficiency when it occurs. There is no special treatment for short stature. It is known that, without treatment, CHH patients have a final height in the range of 110–140 cm.[8] The efficacy and safety of recombinant human growth hormone (rhGH) therapy in CHH is under discussion and there are only a few cases of CHH treated with rhGH described in the literature. The present study therefore describes a case of CHH treated with rhGH.

Correspondence: Monika Obara-Moszynska, MD PhD, Department of Pediatric Endocrinology and Rheumatology, Poznan University of Medical Sciences, 27/33 Szpitalna Street, 60-572 Poznan, Poland. Email: mmoszynska@ump.edu.pl

Received 3 January 2013; revised 24 June 2013; accepted 8 August 2013.

Case report

The female patient was born after an uncomplicated pregnancy in the 40th–41st week of gestation via cesarean section. She had an Apgar score of 9 and her weight was 3000 g. At 6 years of age, she was referred to the genetic clinic due to her short stature, slow development and characteristic complexion. Her predicted height according to her parents was 162.5 cm, which is between the 50th and 25th centile, but since the age of 2 years she had always been beneath the 3rd centile and going down.

At the same time, endocrinologic diagnostics were started. She was diagnosed as having subclinical hypothyroidism on normal ultrasound and negative anti-thyroid antibodies. L-Thyroxine treatment was started. GH deficiency was excluded due to normal GH level in stimulation tests (peak value, 14.8 ng/mL). At the same time, insulin-like growth factor (IGF)-1 concentration was below –2 SD (measured at two different times: 46 ng/mL and 68 ng/mL). On IGF-1 generation test (0.033 mg/kg for 4 days) IGF-1 level rose from 82 up to 202 ng/mL, leading to the clinical diagnosis of inactive GH. Magnetic resonance imaging of the head showed normal pituitary gland. A second visit to the genetics clinic led to an additional diagnosis of CHH, with characteristic radiologic findings in skeletal survey and phenotype such as short stature and fingers, hyperlordosis, as well as light, sparse and bright hair, eyelashes and eyebrows. The patient was 7 years old.

© 2013 The Authors
Pediatrics International © 2013 Japan Pediatric Society

Table 1 Results of 4 year rhGH treatment in the present patient

Time	Height (cm)	Height velocity (cm/year)	Patient age	Tanner stage	BMI (kg/m^2)	Bone age	Height SD	rhGH dose (mg/kg/day)	PAH due to Bayley–Pinneau method (cm)
Start of treatment	112.0	4.0	8 years 9 months	1	18.72	2 years 6 months	–4.00	0.024	NA
After 1 year	119.0	7.0	9 years 8 months	1	20.14	6 years	–3.20	0.022	158
After 2 years	126.5	7.5	10 years 10 months	2	20.8	9 years	–2.85	0.024	147.8
After 3 years	137.5	11.0	11 years 11 months	2	22.06	11 y	–2.23	0.026	146.0
After 4 years	140.9	3.4	12 years 10 months	3	23.93	12 years	–2.63	0.027	150.0
After 4 years 7 months	143.4	4.0	13 years 5 months	4	25.29	13 years	–2.98	0.03	149.7

BMI, body mass index; PAH, predicted adult height; rhGH, recombinant human growth hormone.

Negligible patent ductus arteriosus was found on echocardiography. Because of the lack of hemodynamic disturbance, surgery was not recommended. The patient did not develop infections more often than most healthy children and her immunoglobulin levels were maintained within the normal range. Detailed immunologic diagnostics are planned.

At the age of 8 years 9 months (bone age: 2 years 6 months), she was started on rhGH therapy at a dose of 0.024 mg/kg per day and the effects of this treatment are given in Table 1 and Figure 1. The IGF-1 and IGF-binding protein 3 (IGFBP-3) concentrations during rhGH therapy were within the normal range for age.

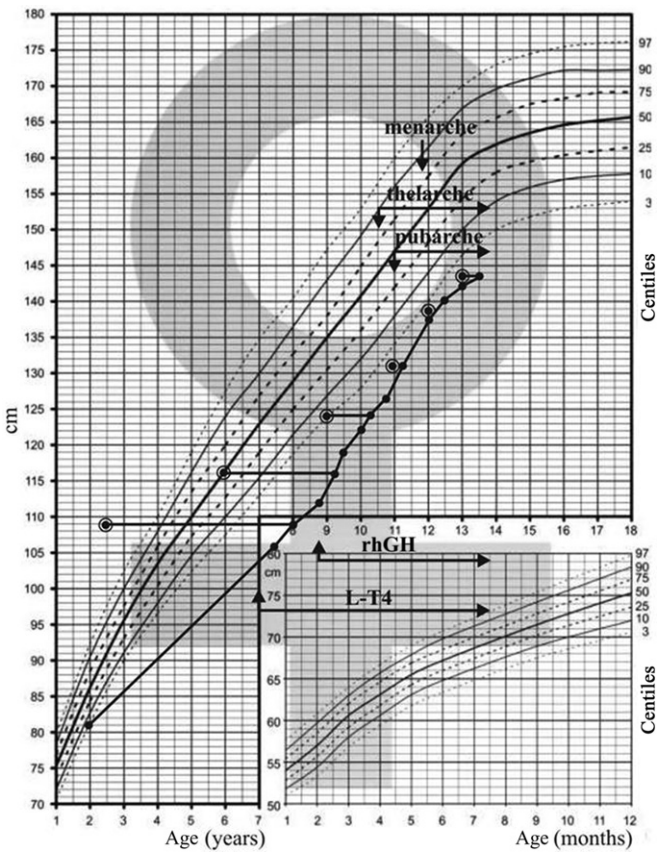

Fig. 1 Growth chart with patient growth pattern. L-T4, L-thyroxine; rhGH, recombinant growth hormone.

During 4 years of treatment, the patient's height improved from –4.00 SD to –2.98 SD, which brought her closer to the 3rd centile. Her bone age, however, approached her biological age, and the height velocity has now significantly decreased. Her predicted adult height (PAH) was very good at the beginning due to retarded bone age. Through the following years, the PAH remained stable.

Discussion

The rhGH treatment had a significant effect on height gain in CHH: the height SD score was changed from –4. to –2.98 by 4 years 7 months of treatment. We expect that the present patient will still grow because the bone age was 13 years at the time of writing. The present patient has already achieved a height of 143.4 cm. rhGH had a significant effect on the height of the CHH patient in the first year of treatment (improved from –4SD to –3.2 SD). In the following years, the height velocity was satisfactory. In the last year, due to the acceleration of bone age, a drop in height velocity was observed. The progress of bone age was probably due to a few factors such as rhGH treatment; early variant of puberty (menarche at age 11 years 8 months); and a tendency of the patient to be overweight. In the present case, the early puberty probably will not have a beneficial influence on final height. The question is, what is the reason for this early development. It could be the result of an individual biological rhythm of growth, but it may also come from a predisposition to obesity, which may affect the time of puberty and accelerate physical development. GH treatment promotes the maturation of bone age, thus it can result in early puberty. In the present patient, the rhGH was probably responsible for the acceleration of bone age, especially during the first 2 years of treatment. The bone age, however, was not more advanced than the chronological age.

Early menarche in the present patient probably was a consequence of several factors already noted, such as individual biological rhythm, overweight and rhGH treatment.

The use of rhGH did not reduce body mass index. Proneness to weight gain and overweight is a characteristic feature of bone dysplasia. The patient is under orthopedic care and no worsening of skeletal abnormalities was registered. Summarizing the advantages of rhGH treatment in the present patient, we can say that rhGH can stimulate height growth and maintain the height SD score at a satisfactory level.

© 2013 The Authors
Pediatrics International © 2013 Japan Pediatric Society

Table 2 Summary of rhGH treatment in CHH

	Patients (*n*/gender)		Age at start of rhGH treatment	Duration of rhGH treatment	Height SD before treatment	Height SD after rhGH treatment	Method of treatment
Harada *et al*.[9]	1/M		3 years	7 years	–4.2	–2.1	rhGH and bone extension
Bocca *et al*.[10]	2 (twins)	M	10 years	2 years	–6.7	Between –2 and –1	rhGH
		F		5 years	–2.9	Between –5 and –4	
	2 (siblings)	F	4 years 11 months	6 years 6 months	–3.9	Between –5 and –4	
		F	7 years 11 months	5 years	–6.6	Between –8 and –7	
Present case	1/F		8 years 9 months	4 years 7 months	–4.0	–2.98	rhGH

CHH, cartilage–hair hypoplasia; rhGH, recombinant human growth hormone.

A 3-year-old Japanese boy had his height improved from –4.2 SD to –2.1 SD with 7 year rhGH treatment along with a surgical leg-lengthening procedure.[9] Compared to the other CHH patients who received rhGH treatment to improve their height, this boy obtained the best result. He was started on the hormone at an early age and his treatment lasted 4 years. It is worth noting that he also benefited from a surgical leg-lengthening procedure. GH was also used to treat two pairs of siblings. A 7-year-old girl and her 4-year-old sister were treated for 5 and 6.5 years, respectively.[10] Finally, a pair of 10-year-old twins, a boy and a girl, were treated for 2 and 5 years, respectively. There was an improvement of 0.2 to 0.8 SD, which was reported during the first year of treatment, but the results were not sustained and the final height has not been improved.[10]

Currently, GH treatment in CHH does not produce strongly optimistic results. It could be a way to maintain height at a certain level (the present patient was dramatically receding from the 3rd centile before being started on rhGH, which brought her back closer to the lower border). This treatment, accompanied by a surgical leg-lengthening procedure, can improve the final height. How the age at the start of treatment and the duration of the treatment affect efficiency is yet to be determined. Table 2 summarizes the reports of the GH treatment results in CHH.

Because of an increased risk of cancer, especially of non-Hodgkin's lymphoma among CHH patients, rhGH treatment must be carefully monitored. The IGF-1 and IGFBP-3 concentrations should also be controlled. The high IGF-1/IGFBP-3 ratio may stimulate the cells to proliferate, increasing the risk of neoplastic disease.

It must be noted that there are different phenotypes of CHH. This might be one of the reasons why the response to treatment differs. The present patient had a milder form: she did not have chronic infections, immunodeficiency or other serious health problems.

Conclusion

Recombinant human growth hormone should be considered as a treatment modality for CHH, only with close monitoring of IGF-1 and IGFBP-3 concentrations, particularly because of the increased cancer risk that is a characteristic feature of CHH.

References

1 Hsieh C-L, Donlon TA, Darras BT *et al*. The gene for the RNA component of the mitochondrial RNA-processing endoribonuclease is located on human chromosome 9p and on mouse chromosome 4. *Genomics* 1990; **6**: 540–44.
2 Topper JN, Clayton DA. Characterization of human MRP/Th RNA and its nuclear gene: Full length MRP/Th RNA is an active endoribonuclease when assembled as an RNP. *Nucleic Acids Res.* 1990; **18**: 793–9.
3 Maida Y, Yasukawa M, Furuuchi M *et al*. An RNA-dependent RNA polymerase formed by TERT and the RMRP RNA. *Nature* 2009; **461**: 230–35.
4 Makitie O, Pukkala E, Teppo L, Kaitila I. Increased incidence of cancer in patients with cartilage-hair hypoplasia. *J. Pediatr.* 1999; **134**: 315–18.
5 Makitie O, Juvonen E, Dunkel L, Kaitila I, Siimes MA. Anemia in children with cartilage-hair hypoplasia is related to body growth and to the insulin-like growth factor system. *J. Clin. Endocrinol. Metab.* 2000; **85**: 563–8.
6 Makitie O, Kaitila I, Svilahti E. Deficiency of humoral immunity in cartilage-hair hypoplasia. *J. Pediatr.* 2000; **137**: 487–92.
7 Makitie O, Kaitila I, Rintala R. Hirschsprung disease associated with severe cartilage-hair hypoplasia. *J. Pediatr.* 2001b; **138**: 929–31.
8 Makitie O, Perheentupa J, Kaitila I. Growth in cartilage-hair hypoplasia. *Pediatr. Res.* 1992; **31**: 176–80.
9 Harada D, Yamanaka Y, Ueda K *et al*. An effective case of growth hormone treatment on cartilage-hair hypoplasia. *Bone* 2005; **36**: 317–22.
10 Bocca G, Weemaes CM, van der Burgt I, Otten BJ. Growth hormone treatment in cartilage-hair hypoplasia: Effects on growth and the immune system. *J. Pediatr. Endocrinol. Metab.* 2004; **17**: 47–54.

© 2013 The Authors
Pediatrics International © 2013 Japan Pediatric Society