Case Report

Diversity of Pubertal Development in Cartilage-Hair Hypoplasia; Two Illustrative Cases

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A B S T R A C T

Background: Cartilage-hair hypoplasia (CHH) is a rare chondrodysplasia, including disproportionate short stature, hypoplastic hair, immunodeficiency, and increased risk of malignancies. Absent pubertal growth spurt and absent pubic hair complicate monitoring of pubertal development in these patients.
Cases: Two CHH patients with delayed puberty and excessive growth failure are described. One of the girls had hypogonadotropic hypogonadism whereas the other had hyponormogonadotropic hypogonadism with no spontaneous pubertal development and slow response to estrogen therapy, both requiring permanent replacement therapy.
Summary and Conclusion: Careful follow-up of pubertal development in individuals with CHH and other growth-restricting bone diseases is needed. In delayed pubertal development timely hormone therapy is essential to ensure maximal growth and well developed secondary sex characteristics.
Key Words: Cartilage-hair hypoplasia, Puberty, Hormone replacement, Hypogonadism, Pubertal induction

Introduction

Normal linear growth comprises 3 phases—infancy, childhood, and puberty—each under unique hormonal control. Childhood growth is driven by the growth hormone insulin-like growth factor axis and pubertal growth is additionally influenced by sex steroids. Skeletal dysplasias affect growth through various mechanisms including impaired growth spurt during puberty.[1]

Cartilage-hair hypoplasia (CHH; Online Mendelian Inheritance in Man 250250) is a rare autosomal recessive metaphyseal chondrodysplasia characterized by severe short-limbed growth failure, hypoplastic hair, immunodeficiency, hematological abnormalities, and increased risk for malignancies.[1,2] The overall mortality attributable to immunodeficiency is increased in all age groups.[3] CHH is caused by mutations in the ribonuclease mitochondrial RNA processing (*RMRP*) gene, encoding the RNA subunit of the mitochondrial RNA processing endonuclease, which is involved in cell cycle regulation.[4] Clinical features might result from a generalized proliferation defect in several cell lines. Median adult height is 122.5 cm and 131.1 cm in women and men, respectively.[1]

There is a paucity of data on puberty and reproduction in patients with CHH. In a series of Finnish women with CHH, spontaneous menarche was reported at a mean age of 13 years (n = 15) consistent with normal pubertal maturation.[1] Pubertal height gain was normal in only 1 case. In a smaller American series (n = 5), mean age at menarche was 14.2 years.[5] Even less is known about pubertal maturation and timing in men with CHH. In a cohort of 11 adult men with CHH, serum concentrations of testosterone, inhibin B, and gonadotropins were mainly normal. However, semen analyses showed impaired spermatogenesis.[6]

Normal pubertal development ensures maximal adult height, well developed secondary sex characteristics, normal sex hormone and gonad function, and normal reproductive capability, all essential for future quality of life. Patients with CHH might encounter various problems related to pubertal maturation and their management might pose a challenge to the caring endocrinologist and gynecologist. We describe 2 illustrative cases of complicated pubertal development in patients with CHH.

Cases

This retrospective single-center study was carried out at Children's Hospital and at Women's Hospital, Helsinki University Hospital, Finland. The study was approved by the Institutional Research Ethics Committee. Hospital records were reviewed for clinical presentation, natural course, growth, laboratory and radiologic investigations, therapy, and outcome. *RMRP* mutations were detected using Sanger sequencing either at Laboratory HUSLAB, Finland, or as a part of previous or ongoing research at Folkhälsan Institute of Genetics, Helsinki.

Pubertal development was assessed according to Tanner. Ultrasound scans of the reproductive organs were

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performed by an experienced gynecologist. Serum concentrations of sex hormones, gonadotropins, and anti-Müllerian hormone (AMH) were examined when considered clinically relevant. In the gonadotropin releasing hormone (GnRH) stimulation test, a 100-μg rapid bolus of GnRH (Relefact; Hoechst, Frankfurt am Main, Germany) was administered intravenously. Serum follicle stimulating hormone (FSH) levels were measured at 0 (immediately before the administration of GnRH), and at 30, 60, and 90 minutes, and serum luteinizing hormone (LH) levels at 0, 20, 30, and 60 minutes. Serum estradiol concentrations were measured with immunochemical assays (AutoDelfia; Perkin-Elmer, or Immulite 2000; Siemens), and AMH was quantitated with an AMH Gen II ELISA (Beckman Coulter, Brea, CA) according to the manufacturers instructions. The limit of quantitation was 0.16 μg/L. Inter- and intra-assay precision was less than 6%, in the range of 3.8-16.5 μg/L.

Clinical and laboratory characteristics of the 2 patients are summarized in Table 1. Both patients were homozygous for the g.70A>G mutation in the *RMRP* gene.

Patient 1

A 14.6-year-old female patient with CHH was referred to the Division of Pediatric Endocrinology because of delayed puberty. She was receiving immunoglobulin replacement therapy. She had severe hypoplastic anemia and required repeated red blood cell transfusions. Splenectomy had been performed at the age of 8.8 years and iron chelation therapy was used for 6.5 years. She had regular medications for asthma and impaired glucose tolerance. On admission, her height was 94.2 cm (11.1 SD), weight was 36.8 kg (body mass index [BMI], 41.5) and pubertal stage M1P1. A GnRH stimulation test showed inadequate FSH and LH responses (Table 1) suggesting hypogonadotropic hypogonadism. Puberty was induced with estrogen therapy (Table 1). Menarche was induced by estrogen-progestin combination therapy after 3 years of single estrogen supplementation. She completed pubertal development and reached Tanner stage M5P4 at the age of 18.8 years. Hormone therapy was paused and a GnRH stimulation test was repeated 4 months later, which showed low FSH and LH responses (Table 1). Ovarian structure and follicle reserve could not be assessed using pelvic ultrasound scan because of obesity. AMH concentration, an indicator of ovarian follicle reserve, was lower than in healthy adolescents. Hormonal replacement therapy was re-started because of menopausal symptoms (hot flushes, sweating, vaginal dryness). Her adult height at the age of 20 years was 95.7 cm (−13.3 SD) and weight 42.1 kg (BMI, 46.0). No pubertal growth spurt could be observed on growth curves and the total height gain during puberty was only 1.5 cm.

Patient 2

A 15.9-year-old female patient with CHH was referred to the Division of Pediatric Endocrinology and Reproductive Medicine because of delayed puberty. She had immunoglobulin A and G subclass deficiency and anemia. Her body hair growth was severely impaired. On admission, her height was 100.9 cm (−10.8 SD) and weight 20.3 kg (BMI, 19.9). She was prepubertal (Tanner M1P1). FSH and LH concentrations were 9.1 IU/L and 0.7 IU/L, respectively. A GnRH stimulation test was performed at the age of 16.3 years (Table 1). The result was considered pubertal despite lower than normal basal LH concentration. Because

Table 1
Pubertal Induction and Clinical and Laboratory Characteristics of the 2 Patients

Age, years	E Dose, mg	Mode of Therapy	Duration of Therapy, months	DDG (10 mg/d), d/month	Pubertal Stage	E2 at Beginning/During Therapy, nmol/L	FSH, IU/L	LH, IU/L	AMH, μg/L	GnRH Stimulation, FSH/LH, IU/L
Patient 1										
14.6	0				M1P1	0.08	1.0	0.29		FSH 1.0-1.2-1.4-1.2/
14.7	0.1	Gel	3		M1P1					LH 0.29-0.68-0.64-0.48
14.9	0.2	Gel	9		M1P1	0.13/−	0.5	0.1		
15.6	0.3	Gel	3		M3P3					
15.8	0.4	Gel	5							
16.3	0.5	Gel	11		M3P3					
17.1	0.6	Gel	6		M4P4					
17.6	0.8	Gel	13	10/mo	M4P4, m+	2.01/0.48	1.6	1.2		
18.8	1	p.o.	7	14/mo	M5P4				0.6	
19.3	Break		4	None			1.9	1.0	0.3	FSH 2.0-2.5-2.4/
19.7	1	p.o.	Cont.	14/mo						LH 1.6-3.7-3.0
Patient 2										
15.9	0				M1P1	0.12	9.1	0.7		FSH 4.7-27.3-37.6-37.2/
16.5	0.1	Gel	3		M1P1	< 0.02/−				LH 0.3-35.3-43.2-47.0
16.8	0.2	Gel	3		M1P1	0.05/−	6.8	0.7		
17.0	0.4	Gel	6		M1P1	0.04/0.18	1.3	0.1		
17.6	0.6	Gel	5		M1P1	0.07/0.09	16.2	5.1		
17.9	1	Gel	3		M1P1	0.2/−	8.0	1.6	0.3	
18.3	0.025 per 24 hours	Patch	8	10/mo	M1P1, m+	0.07/0.14	0.5/0.2	0.0/0.1		
18.8	0.0375 per 24 hours	Patch	6	10/mo	M2P1	0.1/−	0.1	0.1	< 0.2	
19.4	0.05 per 24 hours	Patch	8	10/mo	M2P1					
20.0	1	p.o.	16	14/mo	M2P1	0.55/−			0.4	
20	Break						7.2	1.9		
21.6	2	p.o.	Cont.	14/mo						

Cont., continues; DDG, dydrogesterone; E, estrogen; E2, estradiol; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; m, menarche; p.o., oral; AMH, anti-Müllerian hormone.