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Diversity of pubertal development in cartilage-hair hypoplasia – two illustrative cases

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24 **Abstract**

25 **Background:** Cartilage-hair hypoplasia (CHH) is a rare chondrodysplasia, including disproportionate short
26 stature, hypoplastic hair, immunodeficiency and increased risk of malignancies. Absent pubertal growth
27 spurt and absent pubic hair complicate monitoring of pubertal development in these patients.

28 **Cases:** Two CHH patients with delayed puberty and excessive growth failure are described.
29 One of the girls had hypogonadotropic hypogonadism while the other had hypo-normogonadotropic
30 hypogonadism with no spontaneous pubertal development and slow response to estrogen therapy, both
31 requiring permanent replacement therapy.

32 **Summary and conclusions:** Careful follow up of pubertal development in individuals with CHH and other
33 growth restricting bone diseases is needed. In delayed pubertal development timely hormone therapy is
34 essential to ensure maximal growth and well-developed secondary sex characteristics.

35

36

37 Introduction

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

42
43 Cartilage-hair hypoplasia (CHH; OMIM #250250) is a rare autosomal recessive metaphyseal
44 chondrodysplasia characterized by severe short-limbed growth failure, hypoplastic hair, immunodeficiency,
45 haematological abnormalities and increased risk for malignancies.^{1,2} The overall mortality attributable to
46 immunodeficiency is increased in all age groups.³ CHH is caused by mutations in the ribonuclease
47 mitochondrial RNA processing (*RMRP*) gene, encoding the RNA subunit of the mitochondrial RNA
48 processing endonuclease (RNase MRP), which is involved in cell-cycle regulation.⁴ Clinical features may
49 result from a generalized proliferation defect in several cell lines. Median adult height is 122.5 cm and
50 131.1 cm in females and males, respectively.¹

51
52 There is paucity of data on puberty and reproduction in patients with CHH. In a series of Finnish CHH
53 females, spontaneous menarche was reported at a mean age of 13 years (N=15) consistent with normal
54 pubertal maturation.¹ Pubertal height gain was normal in only one case. In a smaller American series (N=5),
55 mean age at menarche was 14.2 years.⁵ Even less is known about pubertal maturation and timing in CHH
56 males. In a cohort of 11 adult CHH males, serum concentrations of testosterone, inhibin B and
57 gonadotropins were mainly normal. However, semen analyses showed impaired spermatogenesis.⁶

58
59 Normal pubertal development ensures maximal adult height, well-developed secondary sex characteristics,
60 normal sex hormone and gonad function and normal reproductive capability, all essential for future quality
61 of life. Patients with CHH may encounter various problems related to pubertal maturation and their

management may pose a challenge to the caring endocrinologist and gynecologist. We describe here two illustrative cases of complicated pubertal development in CHH patients.

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 by 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 performed by an experienced gynecologist. Serum concentrations of sex hormones, gonadotropins and Anti-Müllerian hormone (AMH) 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), 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 AMH Gen II ELISA (Beckman Coulter®, Brea CA, USA) according to the manufacturers instructions. The limit of quantitation was 0.16 µg/L. Inter- and intra-assay precision was <6%, in the range 3.8 - 16.5 µg/L. Clinical and laboratory characteristics of the two 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 years old female with CHH was referred to 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 SDS), weight 36.8 kg (BMI 41.5 kg/m²) and pubertal stage M1P1. 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 three 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 GnRH stimulation test was repeated 4 months later demonstrating low FSH and LH responses (Table 1). Ovarian structure and follicle reserve could not be assessed by 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 SDS) and weight 42.1 kg (BMI 46.0 kg/m²). 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 years old female with CHH was referred to Division of Pediatric Endocrinology and Reproductive Medicine because of delayed puberty. She had IgA and IgG subclass deficiency and anemia. Her body hair growth was severely impaired. On admission, her height was 100.9 cm (-10.8 SDS) and weight 20.3 kg (BMI 19.9 kg/m²). She was prepubertal (Tanner M1P1). FSH and LH concentrations were 9.1 IU/L and 0.7 IU/L respectively. 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. Since no signs of spontaneous puberty developed, induction was started at 16.5 years (Table 1). During hormone treatment, serum estrogen levels remained low and breast development was constantly poor. Menarche was induced with estrogen-progestin combination therapy 2.5 years after the beginning of puberty induction. Hormone replacement therapy was continued until the age of 21.2 years. After two months' break basal FSH concentration was 7.2 IU/L and LH 1.9 IU/L. Since no spontaneous menstruation appeared and breast development was still poor, hormone replacement was re-initiated. Pelvic ultrasound scans demonstrated

reduced amount of small antral follicles in both ovaries. Serum AMH levels were repeatedly low (Table 1).
Her adult height at the age of 21 years was 104.2 cm (SDS -11.0) and weight 25.2 kg (BMI 23.2 kg/m²).

Summary and conclusions

Very little is known about the potential problems related to puberty in skeletal dysplasias in general and especially in patients with CHH. Here we describe two Finnish CHH patients with delayed puberty. Despite the similar molecular diagnosis, the presentation and treatment outcome of their delayed puberty differed, emphasizing the need for careful endocrinologic and gynecologic evaluation and follow-up.

Patient 1 presented with hypogonadotropic hypogonadism, required induction of puberty and currently continues on hormonal replacement therapy. The etiology of her hypogonadism remains unclear. Severe hypoplastic anemia itself may cause hypothalamic hormonal disturbances. Hypogonadotropic hypogonadism could also be secondary to iron overload caused by repeated blood transfusions. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion and results in hypogonadism. Efficient chelation therapy can benefit endocrine functions in iron accumulation conditions.⁷ However, in our case, despite the therapy for iron overload, hormonal regulation between hypothalamic – pituitary - ovarian axis did not recover. Response to estrogen therapy was considered normal based on breast development and hormone-induced menarche. There are no previous reports on hypogonadotropic hypogonadism in CHH. Our patient had extremely severe growth failure and her pituitary gland dysfunction may be related to unusually severe CHH or to the accompanying immune deficiency.

Patient 2 illustrates a case of partial normogonadotropic hypogonadism with low basal LH levels. This may be result of severe underlying diseases, anemia and immunodeficiency. However, the etiology of poor response to pubertal induction, especially in breast development, remains obscure. Compliance problems are possible during estrogen therapy. However, FSH and LH were mostly suppressed during treatment

indicating adequate compliance. The clinical and laboratory features of CHH suggest a defect in cellular proliferation that affects several cell lines. Limited effect of estrogen therapy in development of breast tissue could be related to defective cellular proliferation. However, endometrium responded well to estrogen therapy. The lack of pubarche may result from impaired germ-cell proliferation in the hair follicles. Lower ovarian follicle reserve and decreased AMH levels have not been described previously in CHH patients and their association with CHH requires validation in future studies. Multidisciplinary care for individuals with CHH helps patients and clinicians to understand the clinical findings and natural course of CHH and to improve the outcome for each patient. Since pubertal development seems to vary considerably in CHH patients, careful follow-up is necessary. If delayed or absent puberty is diagnosed, early and accurate hormonal replacement therapy should be started. Since severe short stature is a major life-long handicap for these patients, it is of utmost importance to optimize longitudinal growth also during pubertal years. Further studies are needed to elucidate the impact of timing of puberty on height outcomes. In both patients, pubertal induction was started with transdermal estrogen therapy which allows smaller dose changes and is especially useful in short stature and low-weight adolescents.⁸

An analysis of health-related quality of life found significantly more problems in patients with chondrodysplasias than in healthy controls, amongst them lower sexual activity.⁹ In a previous series of short statured woman, the overall use of contraception was 42,6 %, almost 50% of whom had tried several contraception methods. This may reflect difficulties in finding a suitable method and highlights the importance of adequate counseling.⁵ Increased incidence of menstrual complications and reduced fertility was more common in all patients with chondrodysplasia.¹⁰ These aspects have not been systematically evaluated in CHH or in other skeletal dysplasias. Similarly, potential pregnancy complications and prenatal care have been poorly described.⁹ In general, women with short stature are at an increased risk of preterm birth, and higher risk of cesarean delivery. In some studies pregnancy loss and fetal complications are more

165 common in short stature women.¹⁰ In treatment and management, special attention should be paid to
166 these issues especially during adolescence and early adulthood.

167

168 Skeletal dysplasia should be considered as a potential contributing factor in short adolescents with
169 disturbed pubertal development. Abnormal skeletal development with premature epiphyseal fusion
170 prevents the use of traditional tools, e.g. bone age and growth curve evaluation, in the assessment of these
171 patients. A multi-professional team including specialist in pediatric and adolescent endocrinology and
172 gynecology could benefit these patients. The paucity of data concerning pubertal development and fertility
173 in CHH and other rare bone diseases calls for more studies.

Author contributions, funding and conflicts of interest

Study design: all authors. Data collection: EH. Data analysis: all authors. Drafting manuscript: all authors. Approving final version of manuscript: all authors.

The authors state that they have no conflicts of interest that could be perceived as prejudicing the impartiality of this case report.

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Age, yrs	E dose mg	Mode of therapy	Duration of therapy mo	DDG (10 mg/d) d/mo	Pubertal stage	E2, nmol/l at beginning / during therapy	FSH IU/L	LH IU/L	AMH ug/L	GnRH stimulation FSH/LH , IU/L
Patient 1.										
14,6	0				M1P1	0,08	1,0	0,29		1,0-1,2-1,4-1,2/
14,7	0,1	gel	3		M1P1					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	M4P4, m+	2,01 / 0,48	1,6	1,2		
18,8	1	p.o.	7	14	M5P4				0,6	
19,3	break		4	none			1,9	1,0	0,3	2,0-2,5-2,4/
19,7	1	p.o.	cont.	14						1,6-3,7-3,0
Patient 2.										
15,9	0				M1P1	0,12	9,1	0,7		4,7-27,3-37,6-37,2/
16,5	0,1	gel	3		M1P1	<0,02 / -				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 / 24 h	patch	8	10	M1P1, m+	0,07 / 0,14	0,5 / 0,2	0,0 / 0,1		
18,8	0.0375 / 24 h	patch	6	10	M2P1	0,1	0,1	0,1	<0,2	
19,4	0.05 / 24 h	patch	8	10	M2P1					
20,0	1	p.o.	16	14	M2P1	0,55			0,4	
20	break						7,2	1,9		
21,6	2	p.o.	cont.	14						

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