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Long-term Outcomes of Patients with Central Precocious Puberty due to Hypothalamic Hamartoma After GnRH Analog Treatment: Anthropometric, Metabolic and Reproductive Aspects

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Summary
Context: Hypothalamic hamartoma (HH) represents the commonest cause of organic central precocious puberty (CPP). Follow-up of these patients at adulthood are scarce.
Objective: To describe the anthropometric, metabolic and reproductive parameters of patients with CPP due to HH before and after treatment with gonadotropin-releasing hormone analog (GnRHa).
Design: Retrospective and cross-sectional study
Setting: Single tertiary center
Participants: Fourteen patients (7 females) with CPP due to HH
Results: The mean duration of GnRHa treatment was 7.7 ± 2.4 yr in boys and 7.9 ± 2.1yr in girls. GnRHa treatment was interrupted at the mean chronological age (CA) 12.1 ± 1.1 yr in boys and 10.7 ± 0.5 yr in girls. At the last visit, the mean CA of the male and female patients was 21.5 ± 3.2 yr and 24 ± 3.9 yr, respectively. Eleven of 14 patients reached normal final height (SDS -0.6 ± 0.9 for males and -0.6 ± 0.5 for females), all of them within target height (TH) range. The remaining three patients had predicted height within TH range. Mean BMI and the percentage of body fat mass was significantly higher in females, with a higher prevalence of metabolic disorders. All patients presented normal gonadal function at adulthood, and 3 males fathered a child.
Conclusion: All patients with CPP due to HH reached normal final or near final height. A higher prevalence of overweight/obesity and hypercholesterolemia was observed in the female patients. Finally, no reproductive disorder was identified in both sexes, indicating that HH *per se* has no deleterious effect on gonadotropic axis at adulthood.

Introduction

Hypothalamic hamartoma (HH) are congenital non-neoplastic malformations constituted of heterotopic hypothalamic tissue located at the base of the cranium, under the third ventricle, next to the tuber cinerium or the mammillary bodies[1]. Clinically, patients with HH can be asymptomatic or manifest a variable endocrine and neurological phenotypes varying from mild to severe clinical manifestation[1]. The main endocrine manifestation of HH is central precocious puberty (CPP) defined as onset of pubertal signs before the ages of 8 in girls and 9 in boys due to early activation of gonadotropic axis [2,3]. HH is the most known organic cause of CPP in both sexes[4].

When symptomatic, together with CPP, patients with HH may also present neurological symptoms such as gelastic epilepsy, focal and generalized seizures, behavioral abnormalities, and cognitive disorders[5,6]. Whole-exome sequencing identified mutations in the Sonic Hedgehog pathway (*PRKACA*, *GLI3*, and large copy number or loss-of-heterozygosis variance of multiple genes involved in this pathway) in 37% of patients with epilepsy due to HH [7].

GnRH analogs (GnRHa) are the first-line treatment for CPP since the 80's[8,9]. However, long-term data of patients with CPP due to HH after discontinuation of GnRHa treatment at adulthood are scarce [10,11]. In this study, we analyzed long-term follow-up of 14 patients with CPP due to HH treated with GnRHa, focusing on anthropometric, metabolic, and reproductive outcomes at adulthood.

Patients and Methods

A retrospective longitudinal cohort study with a cross-sectional evaluation was performed after to be approved by the local Ethic Committee. Written informed consent was obtained from all participants. Since 1996, a total of 28 patients (18 females) with a diagnosis of organic CPP were evaluated and treated in our Endocrine Unit. Fifteen (53.5%) patients (7 females) had the diagnosis of

hypothalamic hamartoma and were treated exclusively with GnRHa and were followed until final or near-final height. One male patient had local reaction to GnRHa and was excluded from analyses.

All medical records of 14 consecutive patients (7 females) with CPP due to HH, who reached their final or near-final height, were systematically revised. Height was considered as final when the growth rate was less than 0.5 cm/yr during the preceding year with bone age (BA) >15 yr in females and >16 yr in males[12].

All patients had pubertal development before the ages of 8 yr in girls and 9 yr in boys, accelerated growth velocity, advanced bone age, and pubertal basal and/or GnRH-stimulated LH levels [3].

Serum LH, FSH, total testosterone and estradiol levels were measured by radioimmunoassay (RIA) until 1991, by immunofluorometric assay (IFMA, AutoDELFIA, Turku, Finland) until 2012 and by electrochemiluminescense assays (ECLIA, Cobas e601, Roche Diagnostics, Indianapolis, IN) after this period. Basal LH > 0.6 IU/L (IFMA) or > 0.3 IU/L (ECLIA) were considered as pubertal levels[13,14]. Progesterone, DHEA-S, and insulin levels were assessed by ECLIA. Androstenedione was assessed by liquid chromatography and mass spectrometry (LCMS-MS). All assays presented intra and inter-assay coefficients of variation < 7%. Pubertal response was considered when GnRH-stimulated LH peak was > 15 IU/L for girls and > 25.5 IU/L for boys (RIA); and > 6.9 IU/L for girls and > 9.6 IU/L for boys (IFMA), and > 8 IU/L (ECLIA)[13,14]. BA was assessed by Greulich & Pyle method[15].

All patients underwent at least one brain magnetic resonance imaging (MRI) study which included pre- and post-gadolinium enhanced sagittal T1-weighted images, as well as coronal T1- and T2-weighted images, with 3-mm slices[16]. HH was diagnosed by the finding of a non contrast-enhancing mass in the tuber cinereum region, isointense on T1-weighted images and iso- or slightly hyperintense on T2 weighted images. HH was classified according to shape as pedunculated (attached to the tuber cinereum without hypothalamus displacement) or sessile (broad-based hypothalamus attachment)[17].

GnRHa (depot leuprorelin acetate 3.75 mg or 11.25 mg) was administrated via subcutaneous or intramuscular, every 28 days or 84 days, respectively. The clinical and laboratory parameters were monitored every 3 months to assess the regression or stabilization of secondary sexual characters, reduced growth velocity and suppressed sexual steroids levels with basal and/or GnRH-stimulated LH levels at prepubertal range (basal LH < 0.6 IU/L for IFMA and <0.2 IU/L for ECLIA; LH 120 min after GnRHa < 4 IU/L) [18]. Bone age was assessed yearly. GnRHa treatment was discontinued when normal puberty would be expected (10–14 yr) and, ideally, when reaching normal height for CA and BA. Predicted height (PH) was calculated using Bayley-Pinneau tables for average BA at the diagnosis and the interruption of GnRHa treatment[19]. Target height (TH) was derived from parents' height measurements and determined by mid parental height minus 6.5 cm for girls and plus 6.5 cm for boys. TH range was established as TH ± 8.5 cm [20,21].

The body mass index (BMI) [weight (kilograms)/square of height (meters)] was calculated using the anthropometric measurements documented in the CHS database. The BMI-SDS was calculated at diagnosis, at discontinuation of GnRHa treatment and at adulthood using the *software* GrowthXP (http://www.growthxp.com/who/demo/index-english.html). Among children and adolescents (< 18 yr), BMI-SDS > 1 and > 2 was used to define overweight and obesity, respectively[22]. For adult BMI calculation, the index of body weight according to the WHO criteria was applied: underweight <18.5 Kg/m^2, normal weight-18.5–24.9 Kg/m^2, overweight- 25.0 –29.9 Kg/m^2, and obesity > 30 Kg/m^2 [23].

The assessment of body composition was measured using multi-frequency bioimpedance analysis (In-Body 720; Biospace, Seoul, Korea). This method analyzes the body composition by

plethysmography multifrequency, which makes body readings using eight electrodes measuring the resistance in five specific frequencies and reactance in three distinct frequencies.

Metabolic parameters were assessed by measurement of fast glucose, insulin, HOMA-IR, total cholesterol and fractions (HDL and LDL), and triglycerides levels. HOMA-IR > 3.80 indicates insulin resistance[24]. Blood pressure was assessed in all patients and hypertension was defined as a systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg.

After the discontinuation of GnRHa treatment, the resumption of menarche, menstrual cycles pattern, underachievement of pregnancy and birth of live fetus were documented in females. Reproductive function in females at adulthood was evaluated by measurement of gonadotropins and estradiol as well as uterine length, and ovarian morphology through pelvic ultrasound at the follicular phase, and progesterone levels at the luteal phase. The polycystic ovarian morphology was defined by the presence of 12 or more follicles of 2–9 mm in diameter and/or an increased ovarian volume > 10 mL (without a cyst or dominant follicle)[25].

Clinical hyperandrogenism signs, including acne (severity and localization), presence and degree of hirsutism (scored by Ferriman-Gallwey scale) were also evaluated. Laboratory hyperandrogenemia was assessed by measurement of DHEA-S, total testosterone and androstenedione serum levels at the follicular phase. Male patients were evaluated through testosterone and gonadotropins serum levels and if they fathered any children.

Statistical Analysis

Statistical analysis was performed using SigmaStat for Windows v.3.5, Systat Software, Inc. Data are presented as mean ± SDS and range. Comparisons among means of continuous variables were calculated using Student's t-test and one-way analysis of variance (ANOVA) followed by Tukey adjustment. Statistical significance was set at $p < 0.05$.

Results

Initial anthropometric and biochemical findings

The mean CA of onset of puberty was 1.8 ± 1.4 yr in boys and 1.6 ± 2.5 yr in girls while the CA at the start of GnRHa treatment was 2.8 ± 2.5 yr in boys and 2.9 ± 2.2 girls. Initial mean BA was 5.7 ± 4 in boys and 5 ± 3.9 in girls. The mean height (SDS) for CA at the start of GnRHa treatment was 2 ± 1.3 for boys and 2.3 ± 1.4 for girls. At the onset of puberty, the mean BMI-SDS was 1 ± 0.8 and 1.9 ± 0.7 in boys and girls, respectively. Clinical and hormonal data at the diagnosis are summarized in the Supplemental Table (Table 1S).

All patients received initially leuprorelin acetate 3.75 mg every 28 days via subcutaneous. Four patients (cases 6, 7, 13 and 14; Table 1S) were switched to leuprorelin acetate 11.25 mg every 84 days, via subcutaneous injection. All patients reached adequate clinical and hormonal control with no need for higher GnRHa dosage. During treatment with GnRHa, clinical and hormonal parameters of adequate pubertal suppression were evaluated quarterly. An adequate clinical control revealed by regression or stabilization of Tanner pubertal stage (assessed by breast development in girls and testicular size in boys) and normal growth velocity for CA was observed in both therapeutic regimens. Additionally, an adequate hormonal suppression, assessed by basal LH and sex steroids as well as GnRH-stimulated LH peak or LH levels 120 min after GnRHa was achieved in all patients considering the criteria mentioned above (data not shown).

Neuroimaging and Neurological evaluation

HH was identified by MRI in all patients and showed distinct size and shape. The HH diameter ranged from 5–30 mm in boys and 4-13 mm in girls. Regarding the shape, five of the 14 HH were classified as pedunculated (2 boys and 3 girls). All patients underwent at least 2 MRI within 4–6 years interval and no changes in their size or shape were identified. Two male patients (2 and 4; Table 1S) and one female (patient 11; Table 1S) had generalized epilepsy and are under antiepileptic therapy (Table 1). Strikingly, only one female patient (patient 11) presented medically uncontrolled progressive seizures, which were initially gelastic (brief spells of laughter) form, evolving to focal and generalized seizures. She underwent surgical treatment (radiofrequency ablation) without complete resolution of seizures. For now, this patient does not present adequate control of seizures even under antiepileptic agents.

Anthropometric data after GnRHa treatment

The mean duration of GnRHa treatment was 7.7 ± 2.4 yr in boys and 7.9 ± 2.1yr in girls. The mean CA at the end of GnRHa treatment was 12.1 ± 1.1 yr in boys and 10.7 ± 0.5 yr in girls, while

mean BA at the end of treatment was 12.1 ± 1.4 yr in boys and 12.2 ± 1 yr in girls. The mean height (SDS) at the end of treatment was 1 ± 1 in males and 1.3 ± 1.2 in females. Interestingly, the mean BMI-SDS at the end of treatment in the males was significantly lower than the females (0.4 ± 1.3 and 2.1 ± 0.7; $p< 0.001$).

At the last visit, the mean CA of the male and female patients was 21.5 ± 3.2 years and 24.5 ± 3.8 yr, respectively. The duration of follow-up from interruption of GnRHa treatment to the last visit was 9.6 ± 3.6 yr for males and 13.6 ± 3.6 yr for females.

Eleven (6 males and 5 females) of the 14 patients reached their final height, while the remaining 3 patients reached their near-final height and were not included in the statistical analysis. Considering only patients who reached their FH, mean total post-treatment growth until reach FH was 22.1± 6.1 cm and 12.3 ± 2 cm in males and females, respectively. The mean FH was 174.5± 6.9 cm (SDS ranging from -1.6 to +1.3) in males and 162.5±5 cm (SDS ranging from -1.4 to +1.1) in females. The FH of all patients was within their TH range. The remaining 3 patients with near-final height also presented predicted height at the last visit within TH range. The comparison among predicted height at the end of GnRHa therapy, FH and TH revealed no statistically significant difference in both sexes (Figure 1).

The mean BMI-SDS did not change from diagnosis to the end of GnRHa treatment in females with HH ($p >0.05$). At adulthood, no males and 4/5 females (80 %) presented overweight or obesity. At the last visit, bioelectrical impedance analysis was performed in 5 males (patients 1, 2, 3, 5 and 7) and 4 females (patients 8, 9, 10 and 11). The mean porcentage of body fat mass for males was 8.5 ± 4.5 % (NR: 10-20%) and for females was 39.3 ± 4.3% (NR: 18-28%).

Metabolic and Reproductive outcomes

Hypercholesterolemia and high LDL levels were identified in one male (patient 1) and 3 females (patients 9, 10 and 11). Insulin resistance was identified in one female (patient 11). Diabetes and hypertension were not observed in this cohort (Table 2).

The mean interval between the discontinuation of GnRHa treatment and the occurrence of spontaneous menarche was 1.6 ± 0.9 yr (ranging from 0.5-3.2 yr). The mean CA of menarche was 12.3 ± 1.4 yr (ranging from 11.2 – 15 yr). All women informed regular menstrual cycles, and no clinical or laboratory evidence of hyperandrogenism was identified. The cross-sectional hormonal analyses performed in the last visit revealed basal serum LH, FSH, estradiol, androstenedione and DHEA-S in women, and total testosterone in both sexes within normal reference ranges for each sex. Pelvic ultrasound showed normal uterine and ovarian volumes in all women. The mean uterine volume was 59 ± 21 cm^3 and right and left ovarian volumes were 5.8 ± 2.7 cm^3 and 7.2 ± 2.9 cm^3, respectively. Only one patient fulfilled criteria for polycystic ovarian (ovarian volume > 10 ml) and 3 patients presented large unilateral ovarian cysts (> 1 cm). Progesterone levels were assessed in all women in the luteal phase and were at ovulatory levels (10 ± 3.5 ng/mL) in all of them. Three male patients fathered children (patients 1, 2 and 3).

Discussion

Long-term follow-up data of patients with CPP due to HH after GnRHa withdraw are rarely reported [9,10]. In the present study, we analyzed the anthropometric, metabolic and reproductive features of 14 patients with CPP due to HH followed in a single tertiary center. The initial manifestation of pubertal signs typically occurred at a very early age, as expected in CPP due to HH, leading to an early initiation of GnRHa treatment. Indeed, all patients had adequate clinical and hormonal suppression of pubertal development even using lower dosage of leuprorelin acetate (3.75 mg monthly or 11.25 mg quarterly). A good compliance, the longer duration of treatment and adequate chronological and bone ages at the interruption of GnRHa contributed to achievement of FH within TH range in both sexes in all patients.

Regarding BMI-SDS and body composition, we observed a sex-specific pattern mainly at adult life. The female patients presented a higher prevalence of overweight/obesity at the start and at the end of GnRHa treatment and at adulthood, evaluated by both BMI and percentage of body fat mass. Similarly, Feuillan *et al.*[10] reported higher BMI in females with CPP due to HH (n=18) compared with patients with idiopathic CPP (n=32) after GnRHa treatment [10]. However, body composition was not evaluated in that study. Familial history of obesity was positive in all but one female and no male patients in our cohort. Therefore, the speculation that HH *per se* has a potential role in the physiopathology of obesity is tempting, but there is no evidence to support it. Moreover, the

increased percentage of total fat mass reported by some authors reinforce the unfavorable effect of GnRHa on BMI and body composition in patients with idiopathic CPP[26–28].

Interestingly, in male patients, overweight/obesity was found in 2 of 7 patients only at the start and at the end of GnRHa treatment. At adulthood, all male patients had normal BMI and normal or low body fat mass percentage. Feuillan *et al*[11] also found a lower frequency of obesity in male patients with CPP due to HH. The reason for this sex dimorphism is still unknown and must be explored in larger cohorts.

As expected, adverse metabolic profile, mainly hypercholesterolemia, was more prevalent in females and can be related to the abnormal high BMI and body fat mass percentage. All other metabolic parameters, such as glucose intolerance, were normal, except in one female patient (patient 11) who presented insulin resistance.

There is a particular interest in reproductive outcomes of these patients in adult life. It has been hypothesized that patients with HH, mainly females, might be at increased risk for post-treatment reproductive disorders due to higher basal and GnRH-stimulated gonadotropins release and earlier age of puberty onset [10,29]. Few studies followed CPP patients due to HH after discontinuation of GnRHa treatment and demonstrated normal recovery of the gonadotropic axis[10,11]. In one study, the comparison of reproductive aspects between 18 girls with CPP due to HH at CA and 32 girls with idiopathic CPP revealed higher LH levels before and at the end of GnRHa treatment in the group with CPP due to HH[10]. Also, it was identified a larger mean ovarian volume, greater BMI, a higher incidence of oligomenorrhea, and neurological disorders in the group with CPP due to HH [10]. Three patients informed the live birth of normal infants. Androgen levels were not assessed in that study. Conversely, in our cohort, all reproductive parameters appraised after interruption of GnRHa were normal, including regular menstrual cycles, normal ovarian morphology and no clinical and laboratory evidence of hyperandrogenism. The higher risk of polycystic ovarian syndrome in CPP patients treated with GnRHa remains controversial[30,31]. In our study, we were not able to evaluate the ovarian morphology systematically through transvaginal ultrasounds and perform quantitative studies on ovarian size, thecae density, number of large follicles, which represents a limitation for the optimal ovarian description.

In another study that included 11 boys with HH after 8.8 ± 3.2 yr of treatment with the GnRH agonist, the testosterone and gonadotropin levels returned to normal 1 yr after pubertal blockage and all of them informed normal sexual relations but none of them desired offspring[11]. Additionally, 2 boys presented punctate echogenic foci suggestive of testicular calcifications [11]. In our cohort, hormonal levels after GnRHa interruption were normal in all 6 males and 3 of them fathered a child.

GnRH and gonadotropin secretion pattern in patients with CPP due to HH in adult life has been little explored and not completely understood. The early activation of gonadotropic axis in childhood is apparently followed by adequate activity at adulthood. We speculated that sexual steroids play an effective negative and positive feedback, allowing regular GnRH and gonadotropin pulsatility in both sexes during adult life. In our study, normal cyclic gonadotropin secretion pattern was detected in females as demonstrated by regular and ovulatory menstrual cycles.

Also, the mechanism by which the HH lead to CPP is not well established. Some hypotheses include the presence of gonadotropin- releasing hormone (GnRH) secreting neurons in the HH or the intrinsic production of transforming growth factor α (TGF-α), an agonist of GnRH secretion, as shown in previous immunohistochemistry studies in animal models[5,32]. In addition, little is known about the molecular etiology of HH and a few studies showed differential gene expression in HH that present with CPP (*IA-1*, *MEF2A*, *mGluR1*, *VILIP-1* and *TSG-6*) compared with those without CPP[33]. The morphology and/or position about other hypothalamic structures represent another element involved in the physiopathology of CPP in these cases[34].

CPP due to HH starts at very early CA (below 4 yr in both sexes), constrasting with the emerging genetic causes of CPP (mainly *MKRN3* mutations), which manifest in a borderline CA (8.2 yr in boys and 6 yr in girls)[1,35,36].

In the current study, 3 of the 14 patients exhibited neurological abnormalities. We previously reported neurological and neuropsychological evaluation of patients from this cohort demonstrating the low prevalence of epilepsy and normal cognition in most patients with CPP due to HH[6]. Epilepsy was present in only 2 males and 1 female patient who are under antiepileptic therapy (Table 1S). Surgical treatment was also performed in one patient due to uncontrolled seizures with medical

treatment. Reported patients with epilepsy, even the less severe forms of refractory epilepsy had significantly lower intelligence quotients (IQ) scores than their counterparts without epilepsy [6].

In conclusion, we presented the longest follow-up of patients with CPP due to HH treated with GnRHa (up to 19.6 yrs in girls and 16 yrs in boys after discontinuation of treatment) including a complete anthropometric, hormonal and metabolic profile. All patients reached normal final height demonstrating the efficacy of GnRHa in preserve potential genetic height. A higher prevalence of overweight/obesity and metabolic abnormalities were observed in female patients. Finally, no reproductive disorder was identified in both sexes, indicating that HH *per se* has no deleterious effect on gonadotropic axis at adulthood.

Conflict of interest statement

The authors have nothing to disclose.

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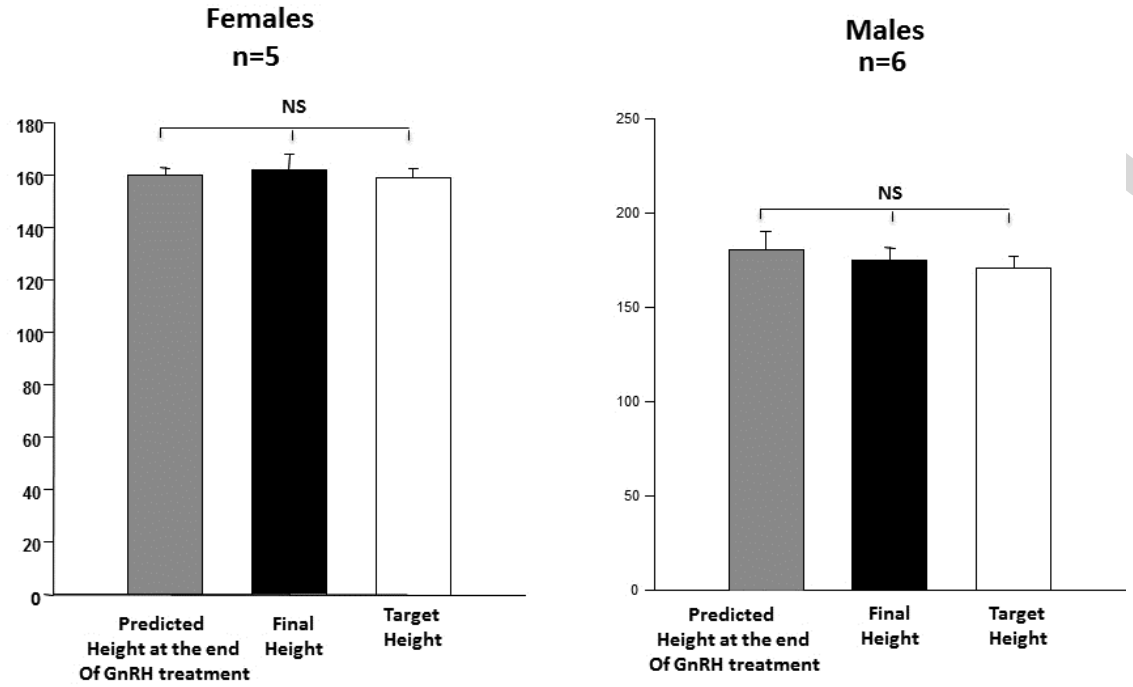
Figure 1



Legends

Figure 1 – Comparison of mean predicted height at the end of GnRHa treatment, mean final height and target height in patients with CPP due to HH (Panel A: females; Panel B: males). There was no statistically significant difference between mean PH, FH and TH in both sexes. NS: not significant.

Table 1. Clinical and laboratory data of 14 patients with CPP due to HH at the end of GnRHa treatment and at adulthood.

	At the end of GnRH-a therapy									At adulthood							
Patients	Sex	Duration of treatment (yr)	CA (yr)	BA (yr)	Height (cm)	Height (SDS)	PH (cm)	BMI	BMI-SDS	CA (yr)	Post Treatment Growth (cm)	FH (cm)	FH (SDS)	TH (cm)	TH (SDS)	BMI (Kg/m^2)	% FM*
1	M	10	12.2	12	157.5	1.1	188.8	18.5	0.4	21.6	16	173.5	-0.2	159	-2.3	20.1	10
2	M	9.1	12.1	12.5	147.5	-0.1	172.9	16	- 1.3	21.2	32.5	180	0.8	175	0	19.4	4.1
3	M	8	14	14	159.6	- 0.13	172.1	16.2	- 1.5	20.9	23.9	183.5	1.3	174	-0.1	18.7	4.6
4	M	5	10.5	11	142	0.37	176.6	20.3	1.6	26.5	21.7	163.7	-1.65	169	-0.8	21.6	-
5	M	3.33	11.7	13.5	157	1.6	174	18.9	0.7	23	14	171	-0.5	177.5	0.4	23.8	16.5
6	M	9	11	12.5	162.4	3.1	190.4	24.3	2.6	-	-	-	-	-	-	-	-
7	M	9.7	11	9.5	150.5	1.3	195.7	16	- 0.1	15.6	24.7	175.2	0.1	169	-0.9	19.1	8.7
Mean		7.7	12.1	12.1	153.8	1	181.5	18.6	0.4	21.5	22.1	174.5	0	171.2	-0.6	20.5	8.5
SDS		2.4	1.1	1.4	6.8	1	9.1	2.8	1.3	3.2	6.1	6.9	0.9	5.8	0.9	1.7	4.5
8	F	9.7	10.7	10.3	138.6	-0.3	158.6	19.2	0.9	20	15.4	154	-1.4	156.7	-0.9	24.8	36.1
9	F	8.6	10.4	13.3	157.2	3	162.5	24.3	1.5	24.8	11.5	169.5	1.2	164	0.3	27.7	36.6
10	F	9	10	12.2	151.5	2.4	162.5	25.4	2.7	24.5	10	161.5	-0.2	157	-0.9	25.3	37.9
11	F	3	11	13	151	1.9	157.6	27.9	2.8	22	12.3	163.3	0.2	158.5	-0.6	31.1	46.7
12	F	9.5	11.8	NA	NA	NA	NA	NA	NA	31.4	NA	164	0.3	165	-1	35.4	-
13	F	8.2	10.9	12.5	140.5	-0.1	149.3	26.5	2.7	-	-	-	-	-	-	-	-
14	F	7.3	10.4	12	146.5	1.2	158.9	23.3	2.1	-	-	-	-	-	-	-	-
Mean		7.9	10.7	12.2	147.5	1.3	158.2	24.4	2.1	24.5	12.3	162.5	0	158.4	-0.6	28.9	39.3
SDS		2.1	0.5	1	6.5	1.2	4.4	2.8	0.7	3.8	2	5	0.8	2.9	0.5	3.9	4.3

CA: chronological age; BA: bone age; SDS: standard deviation; BMI: bodymass index; PH: predicted height (Bayley-Pinneau table for average BA); FH: final height; FM: fat mass; RV: reference value; NA: not available.

*(reference values: for males 10-20%; females 18-28%)

Table 2. Hormonal and metabolic profile of 11 patients with CPP due to HH at adulthood.

Patients	Sex	LH (IU/L)	FSH (IU/L)	T (ng/dL)	E_2 (pg/mL)	DHEA-S (ng/mL)	Δ4 (ng/mL)	P (ng/mL)	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Triglycerides (mg/dL)	HOMA-IR
1	M	7.6	6.2	830	-	-	-	-	152	36	106	48	1.4
2	M	5.9	6.1	812	-	-	-	-	142	52	80	52	NA
3	M	3.1	2.8	716	-	-	-	-	90	42	40	42	0.1
4	M	1.4	2.1	266	-	-	-	-	NA	NA	NA	NA	NA
5	M	9,2	2.7	843	-	-	-	-	106	38	55	31	1.0
7	M	3.4	2.4	467	-	-	-	-	109	38	63	41	1.1
Mean		5.1	3.7	655.7	-	-	-	-	119.8	42.6	68.8	42.8	0.9
SDS		2.7	1.7	216.4	-	-	-	-	23.3	5.6	22.6	7.1	0.5
8	F	4.3	5.2	< 12	76.7	1480	< 0.5	8	143	62	66	74	NA
9	F	2.8	3.9	14	<15	2020	1.1	12.4	257	74	158	127	2.1
10*	F	9.7	5.7	35.5	26.7	195.3	2.6	15.6	216	60	141	74	3.4
11	F	2.9	3	18	123.5	1240	1.1	8.5	144	51	79	72	5.3
12	F	4.8	4.1	13	87	1230	1.7	5.7	187	67	108	59	2.4
Mean		4.9	4.6	18.9	78.5	1233.1	1.7	10	189.4	62,8	110.4	81.2	3.3
SDS		2.5	0.7	11.4	44.1	592.8	0.8	3.5	43.6	7.6	35.1	23.6	1.2
RV		M: 1.7-8.6 F: 2.4-12.8	1.5-12.4	M: 249-836 F: < 48	< 10-122	1480-4070	0.25-2.2	1.7-27	< 200	>45	< 100	< 150	< 3.8

*Under oral contraceptive; T: testosterone; NA: not available; RV: reference value

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