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Growth, development, puberty and adult height of patients with congenital multiple pituitary hormone deficiencies

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ABSTRACT

Objective: Congenital MPHD is a rare condition caused by mutations in pituitary transcription factors genes: PROP1, POU1F1 (PIT1), HESX1, LHX3, LHX4.
Design: We evaluated in a retrospective study the effects on growth and development in 29 patients with congenital MPHD (cMPHD), during hGH replacement therapy alone and combined with sex hormones. Twenty nine patients with cMPHD were included and diagnosed, treated and followed in our clinic from diagnosis to adult age. Measurements on growth and development were taken by the same medical team.
Results: Mean birth weight of 21/29 neonates was 3126 ± 536 g. Mean birth length of 7/29 neonates was 48.7 ± 2 cm. Neuromotor development was normal or slightly delayed. Mean age at referral was 9.5 ± 7 years (m), 6.7 ± 3.5 years (f) ($p = 0.17$). Height (SDS) before treatment was −2.8 ± 1.0 (m), −2.8 ± 1.0 (f) ($p = 0.99$). Mean age at initiation of hGH treatment was 9.9 ± 6.7 years (m), 10.3 ± 4.2 years (f) ($p = 0.85$). Mean age at initiation of sex hormone treatment was 17.0 ± 3.5 years (m), 17.1 ± 2.3 years (f) ($p = 0.88$). Penile and testicular sizes were below normal before and after treatment. Head circumference (SD) was −1.9 ± 0.9 before and −0.6 ± 1.8 at end of treatment ($p < 0.001$). Adult height (SDS) reached −1.1 ± 0.6 ($p < 0.001$) for both males and females.
Conclusion: Despite the multiple pituitary hormone deficiencies including hGH, children with congenital MPHD present with a better auxological development than children with congenital IGHD or congenital IGF-1 deficiency. These findings may be due to irregular and incomplete hormone deficiencies increasing with progressive age and late initiation of puberty.

1. Introduction

Multiple pituitary hormone deficiency (MPHD) refers to impaired production of several anterior pituitary hormones, often including GH. MPHD has an incidence of approximately 1 in 8000 births; about 10–20% of MPHD cases are familial, caused by mutations in the pituitary transcription factors involved in pituitary ontogenesis [1]. These mutations cause congenital MPHD (cMPHD), or, less commonly, an isolated hormone deficiency [2].

The phenotype varies with the transcription factor involved; PROP1 is the most common known genetic cause of cMPHD patients [3], and characterized by somatolactotroph, thyrotroph, gonadotroph and sometimes corticotroph deficiencies and pituitary hyper- or hypoplasia [4]. POU1F1 (PIT1) gene mutation is characterized by somatolactotroph and thyrotroph deficiencies and pituitary hypoplasia [5]. HESX1 gene mutation presents with variable pituitary deficiencies and septo-optic dysplasia [6]. Less frequently are LHX3 mutations having somatolactotroph, thyrotroph and gonadotroph deficiencies and limited head and neck rotation [7]. LHX4 mutations present with variable pituitary deficiencies, ectopic neurohypophysis and cerebral abnormalities [8]. In many of these patients abnormalities were found on skull x-rays [9].

Clinical presentations, including growth deficit, depending on the type of MPHD, severity of deficiencies and on the age at diagnosis [11]. Genital hypoplasia, mainly in males, may result from gonadotropin or GH deficiency [10]. In infants, there is a high risk of hypoglycemia, jaundice and electrolyte disturbances [11]. In older infants and children, the common presenting features include growth failure, a tendency for obesity, disorders of pubertal development and cognitive alterations. Patients with hypothyroidism secondary to a TSH axis deficiency present with signs and symptoms identical to those of primary hypothyroidism, although typically less severe [12].

In the literature, differentiation between congenital and acquired MPHD is not made in most instances, and the clinical presentation for each group is usually not mentioned. The present retrospective report aims to fill this gap, by describing growth and development from birth

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to end of puberty and young adult age in children with congenital MPHD before and during hormone replacement treatment.

2. Subjects

In this historical retrospective study, data on patients diagnosed with cMPHD in childhood were extracted from medical records of the Schneider Children Medical Center. Out of 49 patients with MPHD referred to our clinic between the years 1958–1992, twenty nine patients (14 males, 15 females) with congenital MPHD, including GH deficiency, were identified. The diagnosis of cMPHD was based on one or more of the following criteria: (a) multiple pituitary hormone deficiencies at birth (n = 14) (b) genetic analysis (n = 8) (c) consanguineous families (n = 15) and (d) familial incidence (n = 12). Patients who did not have sufficient follow up data or were suspected to have acquired MPHD (i.e. head trauma, birth asphyxia, breech delivery) were excluded.

2.1. Ethnic origin

The majority of patients originate from the Middle East. The Jewish patients of oriental origin originate from Morocco (n = 9), Tunis (n = 2), Iraq (n = 1), Algeria (n = 1) and mixed (n = 4). The eastern European patients originate from Russia (n = 2), Poland (n = 1), Romania (n = 1) and Czech republic (n = 1). 6 patients originate from mixed origin (Oriental ± European). One Muslim family originates from Israel.

2.2. Consanguinity

Fifteen out of 29 patients belong to consanguineous families and inbred clans, 3 of these families have more than one affected sibling. Consanguinity is seen mostly in the patients of Jewish oriental or Muslim origin.

2.3. Type of deficiency

Fourteen of the 29 patients with cMPHD (10 males, 4 females) had GH, TSH, Gonadotropin and ACTH deficiencies; 10 (3 males, 7 females) had GH, TSH, gonadotropin deficiencies; 3 (1 male, 2 females) had GH, gonadotropin deficiencies, one (female) had GH, TSH deficiencies and one (female) had GH, TSH and ACTH deficiencies.

3. Methods

The pituitary axis was investigated using the following tests: assessment of thyroid function was made by measuring serum TSH and T4 levels [13], deficiency defined as decreased free T4 (<10.8 pmol/l) and concomitantly normal or decreased TSH. GH deficiency was based on GH peak levels less than 3 ng/ml in two GH provocation tests [13,14](sleep, insulin tolerance test [ITT], arginine, clonidine and glucagon tests). All tests were carried out after an overnight fast, and after a euthyroid state has been achieved. IGF-1 measurements were performed when radioimmunoassays became available i.e. during hGH treatment. ACTH deficiency was determined by serum cortisol levels before and after an I.V. injection of 250 μg of ACTH [13]. Gonadotropin deficiency was defined as very low to undetectable levels of LH, FSH, estradiol and testosterone, GnRH stimulation tests [13] were conducted when they became available. Patients were not tested for prolactin deficiency. All patients underwent the same testing protocol according to international standards. The hormonal deficiencies were confirmed after GH treatment with contemporary tools.

Height and length were measured using Harpenden stadiometers. Weight was measured in underwear by a balanced-beam scale in the morning, and in the fasting state. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (meters). Head circumference was measured with a flexible tape. Measurements were standardized to age and sex, and expressed as standard deviation scores (SDS) or SD of the mean. Subscapular skinfold thickness (SST) measurements were taken using a Harpenden Caliper and expressed in mm as recommended by Wells [15]. Penis length (stretched) was measured with a caliper using the norms of Hatipoglu and Kurtoglu [10] and testicular volume with the Prader orchidometer [16] using the norms of Zilka and Laron [17]. Hand and wrist x-rays were preformed periodically to asses bone age using the Greulich–Pyle Atlas [18]. Sex-corrected mid-parental heights were measured based on parental height (measured by the research team) and according to the Tanner method [19]. X-rays (n = 11), CT (n = 12) or MRI (n = 6) of the skull were performed in all patients.

All patients were followed in our clinic at 3–4 months intervals until adult height was reached, defined as growing 0.5 cm/year or less. At each visit they underwent a complete physical examination by the same medical team, including height and length measurements, pubertal staging, before, during and after treatment as well as laboratory chemistry and hormone profiles.

The study was approved by the Hospital Ethics Committee.

3.1. Treatment

Patients with deficient TSH and low T-4 received L-thyroxine before the initiation of hGH treatment. Until 1974 we used pituitary extracted hGH by the Raben method produced in our Laboratory; thereafter commercial preparations of pituitary hGH produced by Nordisk, Serono or Kabi pharmaceutical industries. Since 1992 all patients were treated by recombinant human GH (rhGH) by Novo/Nordisk, Serono, Biotropin or Ferring), administrated by subcutaneously injections in doses of 30–35 μg/kg/day [16]. Puberty was initiated in 27 patients with GnRH deficiency at a mean age of 17, by administration of sex hormone (testosterone enantate starting with a dose of 50 mg/month, progressively increasing it to 200 mg/month in the adult males; to girls, conjugated equine estrogen (CEE) was given until 1990, thereafter Estradiol 1–2 mg/day first alone until feminization was obtained than changed to E2 for 3 weeks and 1 week of progesterone 5 mg daily). The patients diagnosed with ACTH deficiency were treated by hydrocortisone in doses of 5–25 mg/day or in late puberty by prednisone in doses of 5–10 mg/day. Compliance to treatment was checked at each of the visits.

3.2. Statistical analysis

Data was presented as means ± standard deviations (SD). The data were analyzed using BMDP [20]. Continuous variables were compared using Analysis of Variance (ANOVA). In order to determine the effect of treatment we used ANOVA with repeated measures. Pearson's correlations were used to find correlations between various parameters. A p-value of ≤0.05 was considered significant.

4. Results

4.1. Genetic analysis

Four patients of one family with 8 sibling affected were homozygous for the same mutation of PROP1 gene. The defect is a point mutation of C to T transition, resulting in the substitution of arginine (R) to cysteine at codon 120 of the PROP-1 gene (R120C) [21].

4.2. Pregnancy and labor

In 23/29 of pregnancies, information was available on the perinatal period (12 males, 11 females). There were 21 vaginal deliveries, one by forceps and 2 by cesarean section, all without complications. Twenty deliveries were reported to have been full term and two preterm born after the 34th and 36th weeks.

4.3. Birth Measurements

The mean (±SD) birth weight measured in 19 full term neonates (9 males, 10 females) was 3292 ± 510 g (median: 3250, range: 2580–4500 g) in males, and 2949 ± 461 g (median: 2890, range: 2500–3600 g) in females (p = 0.14). Birth length was available in only 7 newborns (4 males, 3 females). The mean (±SD) length was 50.5 ± 0.7 cm for full term males and 48.3 ± 0.6 cm for full term females (range, 48–51 cm, p = 0.007). Compared to all ethnic groups of Jewish populations the birth length was slightly reduced but the birth weight was similar [24].

4.4. Other findings

Five out of 29 patient were born with a midline syndrome (4 with cleft lip and palate and one with a single central incisor) one had a micropenis, 4 had cryptorchidism (2 unilateral, 2 bilateral. All went through orchiopexy), 3 suffered from infantile hypoglycemia and 2 had prolonged jaundice during the neonatal period.

Brain imaging by X ray, CT or MRI was normal in 20 patients, 5 patients had hypoplastic pituitary, 1 patient had flat sella, and 1 patient had a disrupted pituitary stalk.

4.5. Early neuro-motor development

Data on neuro-motor development was obtained from the parents of 18/29 patients. Only in 4 males and 2 females was retardation in all motor milestones ascertained.

4.6. Age at referral

The mean (±SD) ages at referral, at initiation of treatment and length of treatment are shown in Table 1. Two patients started treatment before referral. The delayed referral age is explained by the fact that most patients belonged to new immigrants and/or low socioeconomic families. The mean (±SD) age at present (May 2015) is 44.2 ± 12.5 years for males and 48.3 ± 11.1 years for females (p = 0.35).

4.7. Age at initiation of treatment of the various hormones

Thyroid: 25 patients with various degrees of TSH deficiencies were treated by L-thyroxine in doses adjusted by age and serum free-T4 levels. Before hGH treatment was initiated, the age at initiation of L-T4 ranged between 1 month and 10 years,

GH: 27 patients were treated with hGH replacement therapy, started at a mean age (±SD) of 9.9 ± 6.7 (median: 10.9) years for males, and 10.3 ± 4.2 (median: 11.4) years for females. In all instances normal L-T4 serum levels were ascertained before the start.

Sex hormones: 27 patients were treated with sex hormones, started at a mean age (±SD) of 17.0 ± 3.5 (median: 16.2) years for males, and 17.1 ± 2.3 (median: 17.3) years for females.

ACTH: Partial ACTH deficiency was diagnosed in 12 patients at a mean age (±SD) of 19.4 ± 9.4 (median: 20.2) years for males and 14.0 ± 19.7 (median: 0.1) years for females, and treated by hydrocortisone administration. One patient was treated only during stress conditions.

4.8. Response to treatment

Twenty seven patients (14 males, 13 females) were treated with GH and sex hormones. The findings are summarized in Table 1.

The mean duration of hGH treatment was 8.2 ± 4.8 years (median: 6.8, range 1.8–15.2). The mean yearly growth velocity of 21 patients before the initiation of treatment was 3.9 ± 2.0 cm/year increasing to a mean of 8.7 ± 2.5 cm/year in the first year of treatment in 24 patients. In subsequent years before sex hormone therapy, the growth velocity decreased progressively to a mean of 4.8 cm/year after 4 years of treatment. The mean yearly growth velocity during the first year of sex hormone therapy was 6.2 ± 1.9 cm/year in males and only 2.6 ± 1.9 cm/year in females (p < 0.001), with bone ages of 12.2 and 13.0 years, respectively. In subsequent years the growth velocity decreased progressively to a mean of 1 cm/year after 4 years of treatment, and a mean age of 21.0 ± 2.9 years.

hGH treatment advanced the bone age as evident by a decrease in the chronological age/bone age (CA/BA) ratio, from 1.6 ± 0.4 before treatment to 1.4 ± 0.3 after at least 2 years of treatment, and to 1.3 ± 0.2 during hGH + sex hormone treatment (p < 0.001), more evident in males (Fig. 1).

4.9. Adult height

The adult heights of 27 patients are illustrated in Fig. 2. Ten males and 8 females reached normal heights ranging between the 3rd to 45th centiles. Four males and 5 females had heights below or close to the 3rd centile. The mean height (SDS) increased from −2.8 ± 1.0 to −1.1 ± 0.6 (p < 0.001) for both males and females with no significant difference between the two groups (p = 0.93).

Table 1
Age at referral, start of hGH and sex hormone treatment and response to treatment in patients with congenital MPHD.

		Males (n = 14)		Females (n = 15)		p value
		M ± SD	Range	M ± SD	Range	
Age at referral (years)		9.5 ± 7.0	0.3–21.4	6.7 ± 3.5	1.4–15.1	p = 0.17
Age at initiation of hGH treatment (years)		9.9 ± 6.7	0.5–22.5	10.3 ± 4.2	0.8–16.5	p = 0.85
Bone age at initiation of hGH treatment (years)		6.0 ± 4.4	0.0–12.0	8.0 ± 2.2	3.5–11.3	p = 0.20
Length of treatment (years)		9.8 ± 5.2	1.8–16.5	6.5 ± 3.6	2.1–15.2	p = 0.08
Height SDS	At start of hGH	−2.8 ± 1.0	−4.4 to −0.9	−2.8 ± 1.0	−4.8 to −1.7	p = 0.99
	1st year of hGH Rx	−2.3 ± 0.9	−3.8 to −1.1	−2.6 ± 1.1	−4.0 to −1.3	p = 0.43
Growth velocity (cm/year)	before hGH Rx	4.0 ± 2.7	0.6–9.1	3.8 ± 1.2	1.7–5.3	p = 0.84
	1st year of hGH Rx	9.1 ± 2.8	5.0–13.8	8.2 ± 2.2	4.8–11.7	p = 0.39
	2nd year of hGH Rx	7.2 ± 2.7	4.0–13.5	6.2 ± 2.9	0.1–13	p = 0.39
Age at initiation of sex hormone Rx (years)		17.0 ± 3.5	13.1–23.8	17.1 ± 2.3	13.8–21.9	p = 0.88
Bone age at initiation of sex hormone Rx (years)		12.3 ± 2.1	7.0–16.0	13.0 ± 1.3	11.3–16.0	p = 0.33
Height SDS	At start of sex hormone Rx	−1.9 ± 0.9	−3.5 to −0.5	−1.6 ± 0.8	−3.0 to −0.5	p = 0.38
	1st year of sex hormone Rx	−1.6 ± 0.9	−2.8 to −0.1	−1.4 ± 0.6	−2.5 to −0.5	p = 0.48
Growth velocity (cm/year)	1st year of sex hormone Rx	6.2 ± 1.9	1.5–8.9	2.6 ± 1.9	0.0–5.2	p < 0.001
	2nd year of sex hormone Rx	5.0 ± 2.5	0.5–8.8	1.7 ± 1.3	0.0–5.2	p < 0.001
Adult height	Ht SDS	−1.1 ± 0.6	−0.2 to −2.4	−1.1 ± 0.6	−0.2 to −2.2	p = 0.93
	Ht cm	165.5 ± 6.6	152.5–174.5	153.0 ± 5.6	143–161.6	p < 0.001

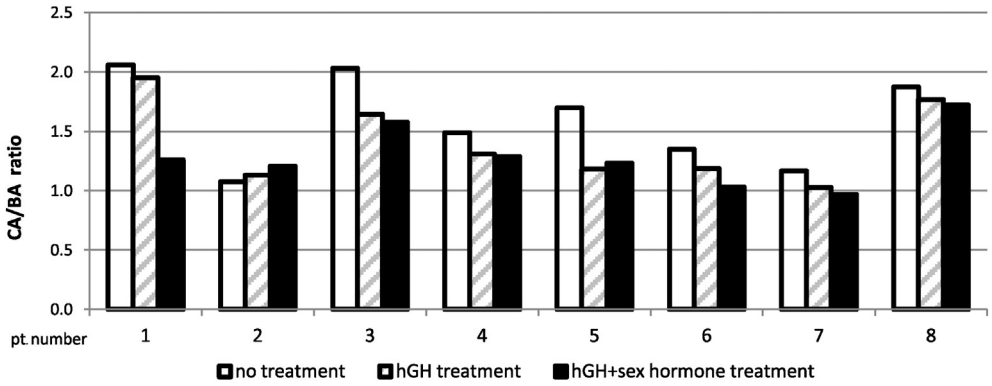

Fig. 1. The ratio between chronological and bone age (CA/BA) of 8 congenital MPHD males before and during hGH and sex hormone treatment.

None of the patients reached the predicted adult height (calculated as sex corrected mid-parental heights) ($p < 0.001$).

There was a negative correlation between age at referral and adult height SDS in females ($r = -0.552$, $p = 0.05$) and between age at initiation of hGH treatment and adult height SDS in the males ($r = -0.525$, $p = 0.065$). A positive correlation was registered between height SDS at referral and adult height SDS in the females ($r = 0.7$, $p = 0.008$). In both males and females there was a positive correlation between height SDS at initiation of sex hormone treatment and the adult height SDS ($r = 0.765$, $p < 0.001$). There was no significant correlation between duration of hGH treatment, bone age and adult height SDS.

4.10. Sexual development

Twenty seven patients (14 males, 13 females) with cMPHD were treated by sex hormone replacement treatment. The sequence of sexual development was closely followed in 11 males and 12 females. Two males had cryptorchidism.

Before sex hormone treatment, axillary hair was present in 12 patients (4 males, 8 females) (mean age of 15.2 ± 2.6 years), and after sex hormone in 14 patients (9 males, 5 females) treatment (mean age of 19.1 ± 4.0 years).

Pubic hair before sex hormone treatment was present in 16 patients (4 males, 12 females) of a mean age of 14.7 ± 2.8 years, and after sex hormone treatment in 13 patients (10 males, 3 females) at a mean age of 17.4 ± 3.7 years.

Breast development in 6 females started at a mean age of 18.3 ± 2.5, and completed (Tanner 5) at a mean age of 23.4 ± 4.4. In 5 females breast development appeared before initiation of sex hormone treatment, probably due to incomplete gonadotropin deficiency.

Mean age at induced menarche was 19.5 ± 2.7 years (range 16.2–25 years).

Full puberty was obtained at a mean age of 23.8 ± 3.4 years in males, and 21.8 ± 3.9 years in females.

Testicular volume measurements were available for 9 males at referral and during hGH treatment (before initiation of sex hormone treatment). All had testicular volumes smaller than normal before treatment, with a mean volume (±SD) of 1.2 ± 0.2 ml. Testicular volume at the end of hGH treatment alone, at a mean age of 15.5 ± 3.1, was 2.2 ± 2.2 ml ($p = 0.21$) (Fig. 3).

Stretched penile length in 9 boys before treatment, during hGH treatment and hGH + sex hormone treatment is illustrated in Fig. 4. Both GH but mainly sex hormone treatment increased penile size. The mean ± SD penile length at end of puberty was 10.7 ± 1.9 cm (range 7–13 cm).

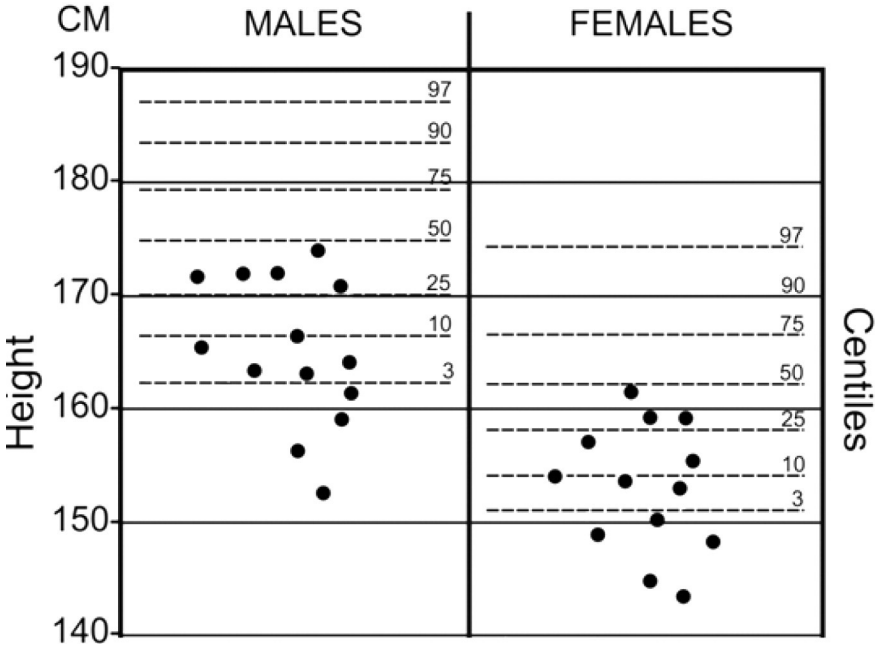

Fig. 2. Adult height of 27 patients with congenital MPHD (percentiles according to Tanner et al. [36].

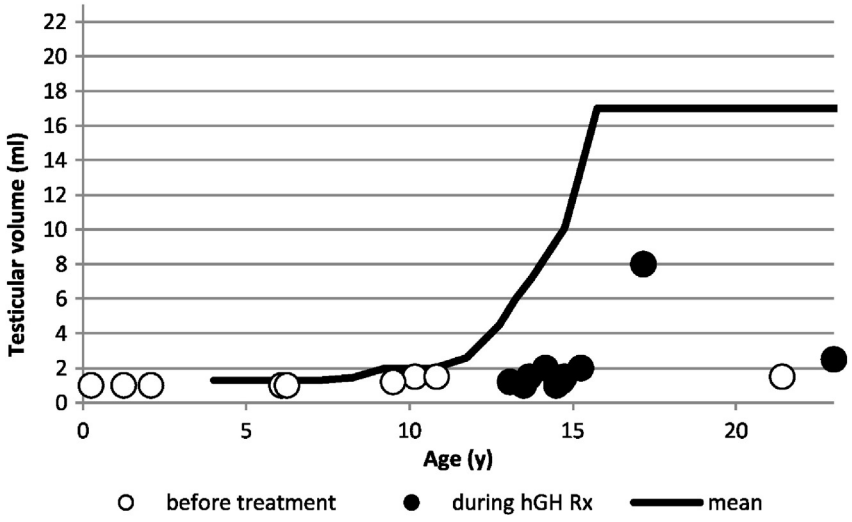

Fig. 3. Testicular volume of 9 males with congenital MPHD before and during hGH treatment, before initiation of sex hormone treatment.

4.11. Head circumference (HC)

Head circumference, denoting brain size, was measured before and during hGH and sex hormone treatment in 13 cMPHD patients. Mean HC (SDS) ± SD before treatment was −1.9 ± 0.9, with 6 patients below −2 SD. During hGH treatment the HC increased to −1.5 ± 1.3, and to −0.6 ± 1.8 during hGH + sex hormone treatment ($p < 0.001$), with no interaction with gender. At the end of hGH and sex hormone treatment, 8 patients had a HC within the normal range, 6 of them above the 50th centile. Four patients had a small head circumference ranging from −2 to −4 SD below the 50th centile.

4.12. Subscapular skinfolds

Consecutive subscapular skinfolds thickness (SST), as a measure of body adiposity, was measured in 19 patients and showed an increase during hGH treatment and hGH + sex hormone treatment. Fig. 5 illustrates the correlation between the duration of treatment and the percent change in subscapular skinfold indicating that longer treatment increases the SST, significantly only in the female group ($r = 0.71$, $p = 0.014$).

4.13. BMI

The mean BMI ± SD before hGH treatment was 16.0 ± 1.4 (median: 16) and after combined therapy 21.9 ± 3.2 (median: 21.9), (similar to IGHD patients [22] − 15.7 before and 20.5 after treatment) both values below those found in Laron syndrome [23].

Knowing that GHD patients have a reduced lean body mass and thinner bones, BMI values are less indicative of the size of the adipose tissue mass.

4.14. Military service

In Israel military service is mandatory in all healthy 18 year old adolescents, we collected data on the enlistment of our patients. MPHD patients are exempt but 12 cMPHD patients (7 males, 5 females) completed military service as volunteers.

5. Discussion

In our retrospective study we aimed to evaluate the growth and development in 29 patients with cMPHD. Only few of the publication

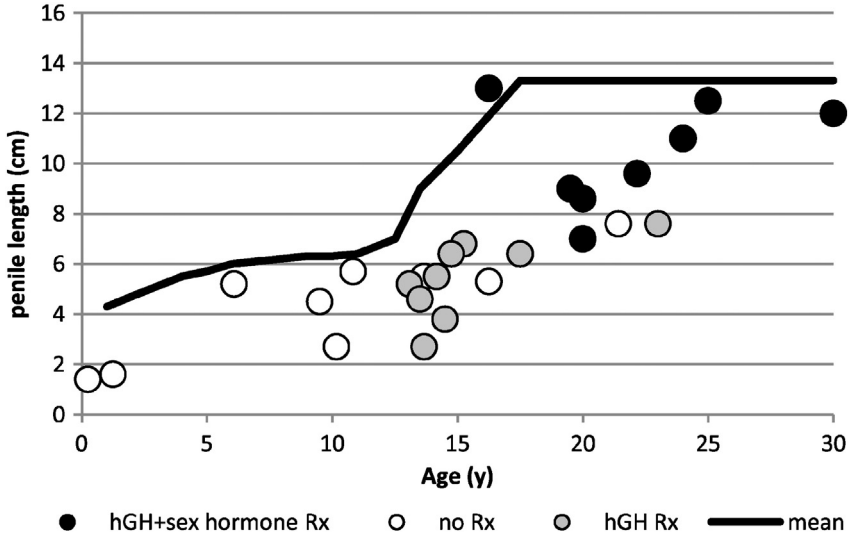

Fig. 4. Penile length of 9 males with congenital MPHD before treatment, during hGH treatment alone, and during hGH + sex hormone treatment.

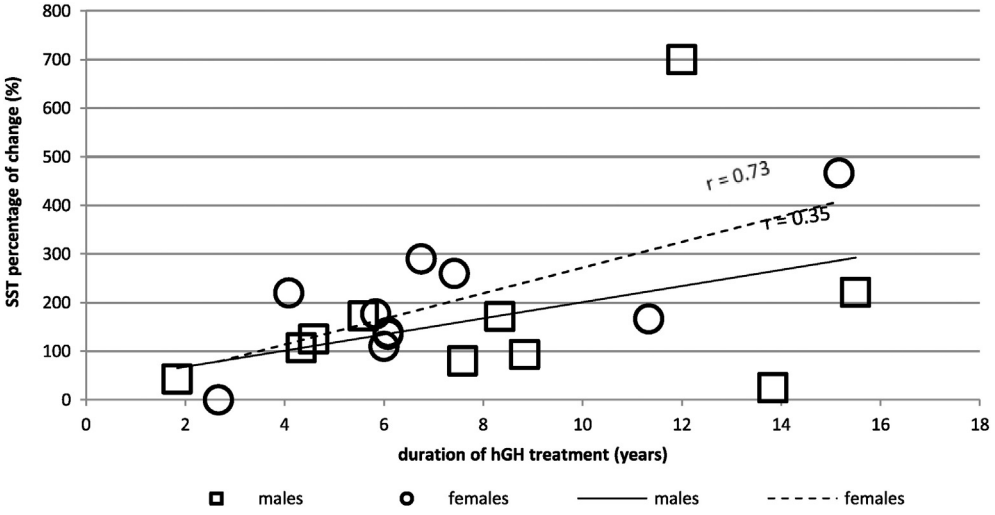

Fig. 5. Percent change in subscapular skinfold thickness (SST) during of hGH treatment.

describing the development and growth of children with MPHD distinguish between the congenital and acquired forms and in those no continuous follow up from infancy to adult age is reported [24,25]. In our study we report on the long term follow up, at short intervals, from early childhood to adult age and evaluation by the same team. The limitations are the heterogeneous composition of our population and the lack of genetic analysis of all patients at diagnosis. Nevertheless their data analysis permitted a number of interesting observations.

It is noteworthy that the degrees of pituitary hormone deficiencies, with the exception of growth hormone, varied between patients and even within the same family [26].

The explanation of the late referral is due to the fact that the majority of families were newly immigrants from mid eastern countries and from a low socio-economic class.

Despite the multiple pituitary hormone deficiencies including severe growth deficiency, the birth length in most full term neonates was greater than that reported in congenital IGHD ($n = 37$) [27] and Laron syndrome [26] IGF-1 deficiency or IGF-R defects [28,29]. So was also the deficit in height in untreated patients at referral and the deficit in head circumference [30].

Of further interest is the finding that the linear height deficit (as expressed height SDS) at initiation of GH treatment in the patients with cMPHD is less when compared to the deficit in height reported by us for cIGHD (-2.8 ± 1 vs. -4.3 ± 1.3 in males, $p < 0.001$, and -2.8 ± 1 vs. -4.5 ± 1.5 in females, $p < 0.001$).

Due to the older age of our patients at initiation of hGH treatment, the growth velocity during the first year of hGH treatment was less than that reported in young children with isolated GH deficiency [31]. Despite the late referral of the patients to our endocrine clinic and late initiation of hGH treatment, more than half reached an adult height within normal growth limits but below the 50th centile. The younger the age of start, the higher the adult height. None of the patients reached the predicted adult height. The taller stature of treated patients with cMPHD than of those with congenital IGHD [22] can be explained by the late induction of puberty, but their adult height is less than that reported for isolated hypogonadotropic hypogonadism [32].

Underdevelopment of the genitalia has been described in several types of hypopituitarism, including MPHD [33]. The small size of the penis and testes in patients lacking gonadotropins alone or in combination with hGH are usually normalized by exogenous administration of gonadotropic hormones [32]. In our study all boys before treatment had small testes within or close to the lower limit of norm for age. During hGH treatment there was only a slight increase in testicular size probably due to the lack of testosterone. Penile size, on the other hand, increased during hGH but mainly during the combined treatment.

At diagnosis, bone age was severely retarded (mean CA/BA ratio = 1.6) as a result of the combined GH and TSH deficiencies in young patients and subsequently due to the deficiency in sex hormones. Replacement therapy even during hGH alone advanced the bone age.

We did not find a difference between genders in the prepubertal age group in growth response to hGH alone, as reported by Cohen et al. [34]. However, we registered a difference between genders during the period of combined GH and sex hormone treatment, the females having a smaller growth response. The significant difference between growth velocities can be explained by the stronger estrogen than testosterone effect on long bone epiphyseal closure leading to earlier advancement of bone age in females. Interestingly, these finding did not influence the adult height which reached a mean of -1.1 ± 0.6 SDS, with no significant difference between males and females.

It has been reported that HC in untreated patients with GHD is disproportionately small [35], and that treatment with GH leads to a quick catch-up in head growth in young (CA < 5 years) GHD patients. In our study, HC showed an increase towards normalization ($SDS = -0.6 \pm 1.8$), especially during the combined GH and sex hormone treatment, denoting that sex hormones enhance the GH effect on brain growth [36].

In conclusion, despite the multiple pituitary hormone deficiencies including hGH, children with congenital MPHD present with a better auxological development than children with congenital IGHD or congenital IGF-1 deficiency (IGF-1 gene deletion and Laron syndrome). Birth length, head circumference and adult height are greater than those in the two above conditions. These findings may be due to irregular and incomplete hormone deficiencies increasing with progressive age and late initiation of puberty.

Conflict of interests

None of the authors has anything to declare.

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