Research Papers

Efficacy of Combined Treatment with Growth Hormone and Gonadotropin Releasing Hormone Analogue in Children with Poor Prognosis of Adult Height

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Objective: *This study was conducted to study the role of combination therapy of growth hormone and Gonadotropin-releasing hormone (GnRH) analogues in girls with idiopathic central precocious puberty (CPP) or idiopathic short stature (ISS).* ***Methods:*** *Five girls with CPP (median age 9.1 y, pubertal stage 2-3) (3 of them previously treated with GnRH analogue (GnRHa) for 16.2 ± 0.3 months) and 8 girls with ISS (median age 11.4 y, pubertal stage 2-3) (previously treated with GH for 10.95 ± 1.42 months), were treated with recombinant human GH (0.33mg/kg/week) and GnRHa (3.75 mg/28 days) for 22 months.* ***Results:*** *Height of girls with CPP improved from –1.3 to –0.2 SDS and height for BA from –2.1 to –0.6 SDS (P = 0.042). Predicted adult height (PAH) improved from –3.1 to –0.6 SDS (P = 0.042). In girls with ISS only PAH improved from –3.0 to –1.5 SDS (P = 0.025).* ***Conclusion:*** *Combined treatment improves height and PAH in CPP. Height in ISS is also improved however not significantly.*

Key words: *Central precocious puberty (CPP), Gonadotropin-releasing hormone analogue (GnRHa), Growth hormone (GH), Idiopathic short stature (ISS).*

GONADOTROPIN-releasing hormone analogues (GnRHa) are used in the treatment of central precocious puberty (CPP) to increase final height with controversial results(1,2) The combination of GnRH analogue with growth hormone (GH) may lead to more satisfactory results by improving the final height in children with precocious puberty and attenuated growth(3,4).

Pubertal growth represents approximately 15-20% of adult height and precedes the fusion of growth plates. Before puberty, growth rate declines with age. This deceleration is compensated by the pubertal growth spurt(5). Nevertheless in girls with precocious puberty, growth acceleration and fusion of the growth plates may be advanced even before the onset of breast development, resulting in impaired adult height(5). When puberty is suppressed with GnRHa, the rate of epiphyseal maturation is decreased as are the GH pulse amplitude and growth rate(2,5).

It is against this background that combined treatment with GnRHa and GH may benefit children with poor adult height potential. The addition of GH to GnRHa treatment may increase the growth velocity and improve the final height in children with CPP. Children with idiopathic short stature (188) and relatively early puberty may also benefit from the combination; by interrupting puberty in order to delay epiphyseal maturation with the hope to gain some centimetres in height.

Subjects and Methods

The study participants consisted of 13 children who were treated with the combination of GH and GnRHa. Five girls were diagnosed with idiopathic CPP and 8 girls with ISS and normal puberty. All children were born full-term appropriate for gestational age and were followed in the Pediatric Endocrine Unit in our hospital. Height, weight and pubertal development were evaluated every

3-6 months. Heights of children and their parents were recorded to the nearest 0.1 cm by a wall-mounted stadiometer with standard counter (Harpenden Stadiometer) at the standing position. CDC charts were used. Subsequent measurements of height were converted into SDS scores using the current CDC reference values as there are no growth charts representing the Cypriot population.

Bone age (BA) was determined according to the method of Greulich and Pyle and adult height was predicted according to the Bayley-Pinneau method. Target height (TH) was calculated according to the method of Tanner(6). Predicted adult height (PAH), height for BA and TH were also converted to SDS. Pubertal development was assessed according to Tanner stages by the same persons (IB, NS) and the initiation of puberty was confirmed by the LH predominant response to LH-releasing hormone (LHRH) stimulation test.

Girls with idiopathic CPP entered puberty before the age of 8 years with breast development at stage 2-3 and pubertal response to LHRH stimulation test. BA was accelerated by two years compared to the chronological age (CA). Pelvic ultrasound showed pubertal findings (increased ovarian volume, number and volume of ovarian follicles and size of uterus) in all girls. MRI of the brain did not reveal any hypothalamic or pituitary abnormality.

The criteria used for the girls with ISS (n = 8) were: (1) short stature with height below –2 SDS, (2) PAH lower than their TH, (3) exclusion of GH deficiency based on normal response to two stimulation tests; glucagon and oral clonidine with peak GH levels >10 ng/mL and (4) exclusion of other conditions such as psychosocial deprivation syndrome. skeletal dysplasias and systematic diseases. All girls with ISS entered puberty at a normal age.

All patients were treated with recombinant human GH at a dose of 0.33 mg/kg/week and GnRHa (triptorelin) 3.75 mg every 28 days.

This study was approved by our institution's ethical committee and informed consent was obtained from the parents of all the girls participating in the study.

Statistical Analysis

Wilcoxon signed rank test with two-related-samples for pre-and post-treatment variables was used for comparing means. $P < 0.05$ was considered statistically significant.

Results

The auxological characteristics of the five girls with idiopathic CPP are shown in *Table I*. Before adding GH, three of the patients were treated with GnRHa alone for a mean duration of 16.2 ± 0.3 months. Patients 3, 4 and 5 were on Tanner stage 3 and started GnRHa treatment at ages 7.5, 9.8 and 3.8 years respectively. Their heights did not improve significantly after 16.2 ± 0.3 months of GnRHa treatment alone (1.1 to 1 SDS, –1.4 to –1.1 SDS and +3.9 to 3.4 SDS respectively). Additionally their bone ages were advanced despite the GnRHa treatment worsening the PAH (10 to 10.8 years, 11 to 11.5 years, 10 to 11 years). Patients 1 and 2 started GnRHa and GH together because of their rapid progression of puberty with advanced BA and very poor PAH. At the start of combined treatment, the median chronological age was 9.1 years and the median height was –1.3 SDS. The patients' median TH was calculated as –0.6 SDS. All females with idiopathic CPP were treated with both GH and GnRHa for a period of 22.8 ± 2.8 months. At the median age of 11.3 years, the median height increased from –1.3 to –0.2 SDS. The median BA advanced by only 0.7 years compared to the CA (median DBA = 2.2).

The median height for BA improved significantly from –2.1 SDS to –0.6 SDS ($P = 0.043$). PAH (median) also improved significantly from –3.1 SDS to –0.6 SDS ($P = 0.042$), resulting in a gain of approximately 9 cm (*Table I*).

The auxological characteristics of the girls with ISS are shown in *Table II*. The mean duration of the combined treatment was 20.75 ± 6.36 months. Patients 3, 5, and 8 were on GH treatment before adding GnRHa for mean duration of 10.95 ± 1.42 months. They were started on GH at ages 9.8, 10.6, and 7.3 years respectively (Tanner stage 1). Their heights had slightly improved (from –3.5 to –3.0 SDS, –3.0 to –2.7 SDS, and –5.8 to –5.3 SDS respectively) while on GH therapy alone. GnRHa was added when they entered puberty in order to

TABLE I–*Auxological Characteristics of Patients with Idiopathic CPP Before and After Combined Treatment with GnRH Analogue and GH*

Pateint no./ sex	CA on start (years)	BA on start (years)	Height on start (SDS)	Height for BA on start (SDS)	Breast stage	PAH on start (SDS)	CA after (years)	BA after (years)	Height after (SDS)	Height for BA after (SDS)	Breast stage	PAH after (SDS)	TH (SDS)
1/F	9.09	11.00	–1.25	–2.07	3	–3.08	11.33	12.00	–1.35	–1.82	2	–1.75	–1.75
2/F	9.41	11.00	–0.33	–1.84	4	–2.41	11.33	13.00	–0.15	–1.48	3	–1.58	–0.58
3/F	8.83	11.00	–1.76	–2.09	2	–3.08	11.60	12.00	0.00	0.48	2	–0.58	–1.40
4/F	10,.08	10.50	0.78	–0.40	2	–1.08	11.00	11.00	0.92	0.92	2	0.25	0.25
5/F	6.50	11.00	–1.80	–2.80	2	–3.30	8.66	11.00	–2.80	–0.58	2	0.08	0.08
Median (range)	9.1 (6.5, 10.1)	11.0 (10.5, 11.0)	–1.3 (–1.8, 0.8)	–2.1 (–2.8, 0.4)		–3.1 (–3.3, 1-1)	11.3 (8.7, 11.6)	12.0 (11.0, 13.0)	–0.2 (–2.8,0.9)	–0.6 (–1.8,0.9)		–0.6 (–1.8, 0.3)	–0.6 (–1.8, 0.3)

CA: Chronological age; BA: bone age; PAH: predicted adult height; TH: target height

TABLE II–*Auxological Characteristics of Patients with ISS Before and After Combined Treatment with GnRH Analogue and GH*

Pateint no./ sex	CA on start (years)	BA on start (years)	Height on start (SDS)	Height for BA on start (SDS)	Breast stage	PAH on start (SDS)	CA after (years)	BA after (years)	Height after (SDS)	Height for BA after (SDS)	Breast stage	PAH after (SDS)	TH (SDS)
1/F	11.66	11.00	–2.76	–1.84	3	–3.58	13.41	12.00	–2.70	–1.21	2	–1.58	–2.08
2/F	11.66	12.00	–2.54	–2.58	4	–2.91	13.90	13.00	–2.75	–1.85	3	–1.41	–1.58
3/F	10.66	10.75	–3.07	–3.20	2	–4.40	13.25	13.00	–2.50	–2.21	2	–2.78	–2.25
4/F	11.50	10.75	–1.99	–2.18	4	–3.40	13.41	12.00	–2.50	–1.14	3	–1.46	–0.38
5/F	11.83	9.25	–2.74	–0.54	3	–1.85	14.58	12.60	–2.75	–1.24	2	–1.59	–1.25
6/F	11.33	7.25	–2.20	0.20	2	–0.25	13.60	10.00	–2.00	0.83	2	0.25	0.27
7/F	10.33	11.00	–2.09	–2.20	3	–2.70	11.90	11.00	–1.35	–0.44	2	–0.91	–0.46
8/F	8.33	6.75	–5.30	–3.30	2	–3.08	12.41	11.00	–3.40	–2.15	1	–3.40	–2.75
Median (range)	11.4 (8.3, 11.8)	10.8 (6.8, 12.0)	–2.6 (–5.3, –2.0)	–2.2 (–3.3, 0.2)		–3.0 (–4.4, –0.3)	13.4 (11.9, 14.6)	12.0 (10.0, 13.0)	–2.6 (–3.4, –1.4)	–1.2 (–2.2,0.8)	–	–1.5 (–3.4, 0.3)	–1.4 (–2.8, 0.3)

CA: Chronological age; BA: bone age; PAH: predicted adult height; TH: target height

avoid BA progression and height deterioration. Just before starting the combined treatment, the median age of all girls with ISS was 11.4 years and their median height was –2.6 SDS. Median TH was –1.4 SDS. After about 20 months of combined treatment (at median age 13.4 years), there was a significant improvement in PAH from –3.0 to –1.5 SDS (P = 0.025) which resulted in a height gain of about 5 cm. Height for BA improved from –2.2 to –1.2 SDS, although this is not a significant improvement (P = 0.238).

Discussion

Our study is a preliminary short-term study based on predicted adult heights in children with two different conditions treated with combination of GnRHa and GH. Predicted height is an important factor which strongly correlates with bone age and can influence final height. Adult height is also affected by other factors such as target height, bone age advancement, the time of onset of puberty and the duration of treatment(2,5). Target height reflects the genetic influence on height, irrespective of pubertal development. The limited effect of GnRHa on final height led to the attempt of using GH as an additional treatment, especially in girls with poor growth prognosis. Similarly, with the hope that the suppression of puberty leads to improvement of final height, GnRH was used as an additional treatment in children currently taking GH for ISS.

Our results show that combined treatment improves PAH in patients with CPP or ISS with poor height potential. PAH improved by 9 cm and 5 cm in CPP and ISS respectively which is a remarkable height gain.

Table III shows the effect on height with combination therapy with GH and GnRHa in different studies(7-19). Majority of the earlier studies using combined treatment in girls with idiopathic CPP, showed encouraging results on the height prognosis as reported in our study(7-10). However only a few published studies were completed until final height was reached, with advantageous results(9,10). On the contrary others found no significant increase in final heights despite the previous increase in predicted heights(11,12). Some studies showed beneficial effect in girls with early puberty(13,14). Controversial results were also observed on children with ISS treated with GnRHa and GH. Combined treatment increases predicted adult heights in short girls without GH

TABLE III-*Different Studies(7-10) for the Use of Combined Treatment in Patients with Central Precocious Puberty and Idiopathic Short Stature*

Reference	Diagnosis	No of Patients	Duration of treatment (years)	Height gain (cm)
Job, Horm Res 1994	CPP/EP	30	3	6.9
Saggese, Acta Pediatr 1995	CPP/GHD	12	1	3.7 ± 0.2
Pasquino, JCEM 1999	CPP	10	2-3	7.9 ± 1.1
Tuvemo, Acta Pediatr 1999	CPP/EP	46	2	2.7
Pucarelli, JPEM 2003	CPP	17	2-3	12.7 ± 4.8
Mul, Clin Endocrinol 2005	EP	14	3	8.2 ± 3.7
Volta, J Endocrinol lnv 1993	ISS	18	1	0
Saggese, J Pediatr 1995	ISS	7	2.01 ± 0.52	6.1 ± 1.2
Tanaka, JPEM 1997	ISS	21	3.2-4.8	3-5
Lanes, Clin Endocrinol 1998	ISS	10	2	0.3 ± 2
Pasquino, JCEM 2000	ISS/EP	12	4.6 ± 1.7	10 ± 2.9
Balducci, JCEM 2001	ISS	10	2-3	1-4
Kamp, JCEM 2001	ISS	18	3	8-10.4

CPP = Central precocious puberty, EP = Early Puberty, ISS = idiopathic short stature, GHD = Growth hormone deficiency

What is Already Known

- Combined treatment with GH and GnRH analogue in girls with idiopathic CPP and ISS may have satisfactory results on the height prognosis.

What this Study Adds

- Combined treatment improves PAH in patients with CPP and ISS with poor height potential improving PAH by 9 cm and 5 cm respectively.

deficiency, entering puberty at a normal age(15). Other studies showed improvement on PAH in children with ISS or IUGR(16) while some others found no or minor effect on PAH in patients with ISS and normal puberty(17-19).

The limited number of the patients and the lack of randomized blinded prospective trials do not allow a thorough analysis of the results but the available evidence suggests a beneficial effect of combined treatment on PAH. The majority of patients were treated for a short period of time (less than 3 years) and some of them started late or treated with either GH or GnRHa at the first place depending on the growth disorder they had. PAH may improve with early initiation and longer duration of therapy. Definite conclusions will arise after the patients reach their final heights. However we should always consider the economical and ethical cost of such therapies, which must be limited to very short subjects with very poor growth prognosis.

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