Case Reports

Growth Hormone and GnRHa Combination Therapy in the Management of Precocious Puberty

V.V. Khadilkar
A.V. Khadilkar
G.B. Maskati

Growth hormone when used in precocious puberty in combination with Gonadotropin releasing hormone analogue (GnRHa) instead of using GnRHa alone has been shown to improve final height prognosis. We report here a two-year follow-up of three cases of precocious puberty, two of whom were treated with a combination of GH and GnRHa and the third treated with GnRHa alone.

Key words: *GH, GnRHa, Precocious puberty.*

Precocious puberty may lead to short stature due to the premature fusion of epiphyseal growth plates(1). In Central precocious puberty (CPP) Gonadotropin releasing hormone analogue (GnRHa) has been used to halt the progress of puberty and postpone premature fusion of the epiphysis(2). With this treatment the growth velocity (GV) often becomes subnormal. To combat this situation Growth hormone (GH) has been used simultaneously with GnRHa to improve final height prognosis(3). Reports of the combined use of GnRHa and GH in patients with CPP are scarce in Indian literature. We report a two-year follow-up of three cases of CPP, two treated with GH and GnRHa and the third treated with GnRHa alone.

From the Growth and Pediatric Endocrine Research Unit, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, 32, Sassoon Road, Pune-411001.

Correspondence to: Dr. Vaman Khadilkar, Consultant Pediatric Endocrinologist, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, 32, Sassoon Road, Pune-4110001. E-mail: akhadilkar@vsnl.net, vkhadilk@vsnl.com

Manuscript received: December 15, 2003;
Initial review completed: March 1, 2004;
Revision accepted: June 15, 2004.

Case Reports

The clinical spectrum of the three patients with precocious puberty is depicted in *Table I*.

Case 1: A 7½-year-old girl, operated for hydrocephalus at 3.8 years, presented with history of breast development of 8 months duration. Her mid-parental height (MPH) was 157 cm, height was 115 cm (just below 25th centile, Agarwal charts(4)) and weight was 17 kg (10th centile). Her sexual maturity rating (Tanner staging) was axillary hair 1, pubic hair 2, breast stage 3 and no menses. Her bone age was 9.8 yr and her GV was 8.3 cm/year (Normal GV 5 cm/yr). The presence of a previous CNS pathology and clinical findings on presentation lead to the clinical suspicion of the diagnosis of central form of isosexual precocity. Leutinising hormone (LH) was 6.2 miu/mL (normal <1 miu/mL), follicle stimulating hormone (FSH) was 3.0 miu/mL (<1 miu/mL) and LH/FSH ratio was 2.1 (normal prepubertal <1), prolactin was 7.5 ng/mL (2-15 ngm/mL), estradiol was 80 pg/mL (normal prepubertal < 10 pg/mL) and she was euthyroid. Pelvic ultrasound showed adult-type uterus. Both ovaries showed 3-4 follicles

TABLE I–*Patient Characteristics.*

Characteristics	Patient 1	Patient 2	Patient 3
Age in years at the beginning of SSC*	6.8	7	4.8
Presenting complaints	Thelarche	Menarche	Thelarche
Etiology	Hydrocephalus	Hydrocephalus	Idiopathic
MPH	157	158	146
Height sds - pretreatment	0-0.94	1.16	–0.17
Tanner staging - pre treatmentA1P2B3M0**	A3P4B4M1	A1P1B3M0	
Bone age	9.8	13.2	9.2
Uterus length, shape	5 cm, Pear	6 cm, Pear	4.5 cm, Pear
Ovarian volume (right, left)	1.2, 1.2	1.8, 2.2	1.2, 1.2
GnRHa (Tryptorelin) dose	100 Microgm/kg	100 Microgm/Kg	100 Microgm/Kg
Growth hormone dose	20 iu/m^2	20 iu/m^2	0
Predicted height before treatment	132 cm	139 cm	155 cm
Predicted Height after treatment	138 cm	149 cm	158 cm

* Secondary sexual characteristics; ** A - axillary hair, P - pubic hair, B- breast development, M - Menarche.

and were 1.2 mL in volume. Neuroimaging showed the shunt in place and a normal pituitary gland. She was treated with GnRHa (Tryptorelin 100 Microgm/Kg) intramuscularly, as a monthly injection for a period of 2 years and GH in the dose of 20 iu/m^2/ week. Final height prediction done by the Tanner Whitehouse 3 method(5) was 132 cm. After 3 months of therapy there was regression of all signs of puberty, and hormones showed prepubertal values. GV dropped to 6 cm per year. After 2 years of treatment, puberty was still suppressed and her height was 127 cm, weight was 23 Kg, bone age was 10.4 years, height SDS was –0.74 and final height prediction improved to 138 cm.

Case 2: A 9-year-old girl presented with history of regular menses for 6 months, height was 136 cm, and weight was 30 Kg, both above 75th centile for age. Her MPH was 158 cm, her GV was 13.5 cm /year (Normal GV 4-5 cm/year) and bone age was 13.2 years. Other clinical findings and treatment were similar to case 1. Final height prediction was 139 cm. Three months after therapy puberty was suppressed and GV dropped to 6 cm/year. After two years of treatment her height was148 cm, weight was 34 Kg, bone age was 14.2 years, height SDS was 0.93 and final height prediction improved to 149 cm.

Case 3: A 4-year-old girl presented with bilateral breast development for 3 months. Her MPH was 146 cm, height was 100.3 cm (50th centile), weight was 13 Kg (just above 3rd centile), GV was 8.6 cm/year (Normal GV 5 cm/year) and bone age was 9.2 years. Other findings were similar to case 1. Her final height prediction was 155 cm. She was treated with GnRHa as above. Economic constraints did not allow GH therapy. Her GV declined to 3.6 cm/year. At the end of 2 years of treatment her height was 109.5 cm, weight was 15 Kg, bone age was 10.4 years, height SDS was

–0.64 and final height prediction was 158 cm.

Discussion

Precocious puberty is of concern as it may result in short adult stature due to rapid skeletal maturation attributable to early secretion of sex hormones, and the psychosocial difficulties that the sexually precocious child encounters(6). Effective management depends on identification and treatment of the cause and also the arrest of progression of puberty. In CPP, the pubertal hypothalamo-pituitary-gonadal axis can be inhibited by the administration of a long acting analogue of GnRH. While on therapy with GnRHa bone age progression is slowed and thus there is a potential to extend the time available for pre-pubertal growth(1).

Kaplowitz has reasoned that while on treatment with GnRHa, improvement in adult height has been disappointing because the benefit of slower bone age advancement is offset by slower than normal linear growth once sex steroids are suppressed(7). Pucarelli, *et al*. have treated 35 girls (who have now reached adult height) with CPP with GnRHa for 2-3 years whose GV fell below the 25th percentile for age, 17 of these received GH in addition. It was concluded that patients treated with combination therapy showed an adult height significantly higher than pretreatment predicted adult height, while adult height of patients on therapy with GnRHa alone was not significantly higher than pretreatment predicted adult height(8). They have also commented in an earlier paper that GnRHa decreases GV so markedly as to impair predicted adult height to below the third percentile(9).

GV during GnRHa therapy given alone may often decline to subnormal levels thus reducing the advantage of treatment in terms of final height achievement. A combination of GH and GnRHa is hence suggested which may lead to a better adult height. Exogenous GH replaces the secretion of endogenous GH, which gets suppressed with GnRHa treatment(3).

A major consideration in India is the cost of therapy as GnRHa given alone costs about Rs. 4000/month, when GH is added to therapy it costs an extra Rs. 20,000 - 25,000/month.

In our 3 patients, we have demonstrated that GnRHa, is effective in arresting the progress of puberty but as our case 3 shows, when GnRHa used alone, the GV reduces to less than normal pre-pubertal levels, thus compromising final height prognosis (*Table II*). We demonstrated in our first two cases that the decline in GV following GnRHa therapy to levels below normal was prevented with the use of GH, thus improving final height potential.

TABLE II–*Comparison of Height Velocity*

Case No.	*Pre-treatment*	*Post-treatment*
1. GH + GnRHa	8.3	6.0
2. GH + GnRHa	13.0	6.0
3. GnRHa alone	8.6	3.6

Contributors: VVK and AVK carried out the clinical workup. AVK and GBM collected the data and drafted the manuscript. VVK will act as guarantor of the study.

Funding: HCJMRI, Jehangir Hospital, Pune.

Competing interests: None.

REFERENCES

1. Menon PS. Precocious Puberty. In: Pediatric Endocrine Disorders, 1st edn. Eds. Desai MP, Bhatia V, Menon PS. Chennai, Orient Longman, 2001; p. 138-153.
2. Pasquino AM, Municchi G, Pucarelli I, Segni M, Mancini MA, Troiani S. Combined treatment with gonadotropin-releasing

hormone analog and growth hormone in central precocious puberty. J Clin Endocrinol Metab. 1996, 81: 948-951.

3. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. Pediatrics. 1999, 104: 1010-1014.
4. Agarwal DK, Agarwal KN, Upadhyay SK, Mittal R, Prakash R, Rai S. Physical and sexual growth pattern of affluent Indian children from 5-18 years of age. Indian Pediatr. 1992, 29: 1203-1282.
5. Tanner JM, Healy MJ, Goldstein H, Cameron N. Prediction of Adult Height TW3 equations. *In:* Tanner JM, Healy MJ, Goldstein H, Cameron N, Editors. Assessment of Skeletal Maturity and Prediction of adult height by TE3 method, 3rd edn. London, W.B. Saunders, 2001; p 26-43.
6. Root AW. Precocious Puberty. Pediatr Rev 2000, 21: 10-19.
7. Kaplowitz PB. If Gonadotropin-Releasing Hormone Plus Growth Hormone (GH) Really Improves Growth Outcomes in Short Non-GH-Deficient Children, Then What? Clini Endocrin and Metab 2001, 86: 2965-2968.
8. Pucarelli I, Segni M, Ortore M, Arcadi E, Pasquino AM. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: A further contribution. J Pediatr Endocrinol Metab 2003, 16: 1005-1010.
9. Pucarelli I, Segni M, Ortore M, Iannaccone R, Pasquino AM. Combined therapy with GnRH analog plus growth hormone in central precocious puberty. J Pediatr Endocrinol Metab 2000,13: 811-820.

Megalencephalic Leukoencephalopathy with Subcortical Cysts

K. Hari Krishnan
C. Leema Pauline
G. Kumaresan
T.K. Vasantha Mallika

Megalencephalic leukoencephalopathy with subcortical cysts is a rare disease first described in 1995. It is characterized by macrocephaly and early onset white matter degeneration. We report two siblings who were diagnosed to have this disease. This disease must be included in differential diagnosis of macrocephaly with early onset leukoencephalopathy.

Key words: *Macrocephaly, Megalencephalic leukoencephalopathy, Subcortical cysts, White matter degeneration.*

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), also known as van der Knaap's disease, is characterized by early-onset macrocephaly, with mild motor developmental delay and seizures; gradual onset of ataxia, spasticity, and sometimes extrapyramidal findings; and usually late onset of mild mental deterioration.

Macrocephaly is present at birth or develops during the first year of life. The degree of macrocephaly is variable and can be as much as 4-6 SD above the mean. Almost all patients have epilepsy from an early age. Some patients have died in their teens or twenties but others are alive in their forties.

From the Department of Pediatrics and Department of Pediatric Neurology, Institute of Child Health and Hospital for Children, Chennai, India.

Correspondence to: Prof. G. Kumaresan, B-9, 26, Desika Road, Mylapore, Chennai 600 004, India.

Manuscript received: December 10, 2003;
Initial review completed: January 29, 2004;
Revision accepted: July 26, 2004.