Age at menarche and near final height after treatment with GnRHa alone or combined with GH in Korean girls with central precocious puberty

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INTRODUCTION

• GnRHa therapy was reported to suppress gonadal steroid effectively enough to delay menarche until an appropriate age and developmental stage. But enhancing the final height has been so controversial that an additional approach has been used. In this approach, GH is used to promote growth velocity during the slow phase of growth during GnRHa treatment, and aromatase inhibitors are administered to try to delay estrogen-induced closure of the growth plate. This "belt and braces" approach may be beneficial in some cases, but there has been no controlled trials of its efficacy with respect to adult height (AH).

• The aim of our study was to evaluate the age at menarche after the discontinuation of GnRHa and the statural growth outcomes in girls with CPP who were treated with GnRHa with or without GH.

SUBJECTS AND METHODS

• Retrospective analysis of 85 idiopathic CPP girls treated with GnRHa from 2002 to 2012 and attained near final height (NFH) after menarche.

• 24 patients were treated with additional GH (predicted AH (PAH) < 5th percentile at the start of GnRHa, if the parents wanted)

• GnRHa dose : 75–150 μg/kg q 4 wk until 11.5–12 yr of BA, and additional GH dose : 0.6–1.0 IU/kg in 5–7 divided doses weekly.

• An LH level < 3 IU/L at 30–60 minutes after GnRHa injection was considered adequate suppression at 6 mo of treatment.

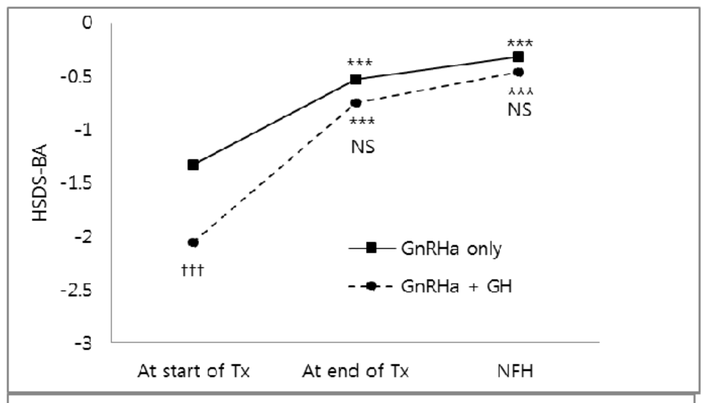
• Bone age (BA) by Greulich-Pyle method, Predicted adult height (PAH) by Bayley-Pinneau method, Near final height (NFH) by PAH at the last follow-up visit after menarche with a BA over 13.5 yr, Midparental height (MPH) as the average of the parental heights minus 6.5 cm.

•For the comparison of auxological differences and growth-promoting effects, the subjects were classified into two groups, treated with GnRHa only (N = 61) and treated with GnRHa plus GH (N = 24).

RESULT

	GnRHa alone (N=61)	GnRHa + GH (N=24)	*P*-value
At the start of GnRHa treatment			
CA (yr)	8.2±0.8	7.9±0.7	0.085
BA (yr)	10.5±1.1	10.4±1.3	0.732
MPH (cm)	158.4±3.4	156.3±3.2	0.001
HSDS for CA	0.9±1.0	0.3±1.3	0.008
HSDS for BA	-1.3±0.9	-2.1±1.1	0.001
PAH (cm)	153.7±7.4	147.7±8.0	0.000
At the end of GnRHa treatment			
CA (yr)	10.2±0.7	10.4±0.7	0.364
BA (yr)	11.5±0.7	11.7±0.8	0.201
HSDS (CA)	0.8±0.8	0.5±1.0	0.229
HSDS (BA)	-0.5±0.8*	-0.7±0.8*	0.234
PAH (cm)	159.2±5.7†	157.7±5.4†	0.277
At menarche			
CA (yr)	11.5±0.8	11.8±0.7	0.151
after Tx end (mo)	15.3±6.6	16.8±6.3	0.333
Duration of treatment			
GnRHa (yr)	2.0±1.0	2.5±0.9	0.059
GH (yr)	-	2.1±1.1	-
At the last follow-up			
CA (yr)	12.5±1.0	12.6±1.0	0.568
BA (yr)	14.5±1.0	14.4±1.0	0.573
HSDS for CA	0.8±1.0	0.4±1.0	0.157
HSDS for BA	-0.3±0.9*	-0.5±1.0*	0.505
PAH (=NFH, cm)	160.0±4.9†	159.1±4.9†	0.412
Assessment of height increment			
Δ PAH (T1~T2)	4.4±5.0	4.0±4.1	0.690
Δ PAH (T2~Te)	6.3±3.3	11.4±3.8	0.000
Δ PAH (T1~Te)	0.8±3.6	1.3±3.1	0.460

Table 1. Auxological data of the subjects with central precocious puberty (N = 85) divided into two groups.
- At the start of treatment, the CA and BA were not different between the two groups, but MPH, height, and PAH were significantly shorter and HSDS adjusted for both CA and BA was significantly lower in the combined group.
- At the end of GnRHa treatment and at NFH, all the parameters including height, HSDS for CA and BA and PAH were not statistically different.



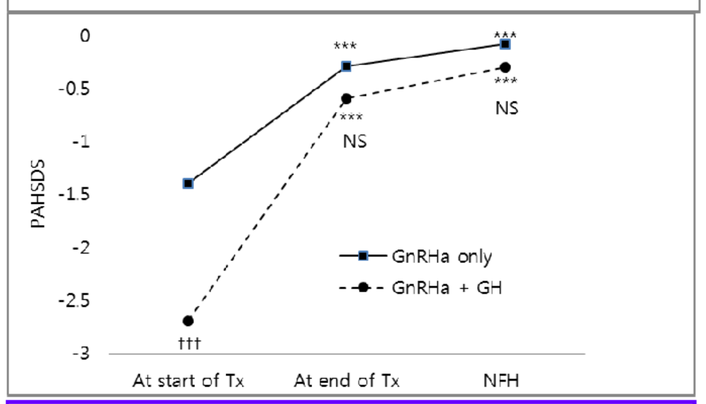


Figure 1. changes of Height SDS for BA and PAH.
At start of therapy the HSDS-BA and PAHSDS were significantly different between GnRHa group and combined , but the difference became insignificant during treatment and at near final height.(NFH).

Table 2. Multiple linear regression analysis between growth parameters and NFH.

	Near final height			
	β	SE (β)	T	*P*-value
CA at Tx start	-3.233	1.433	-2.256	0.028
Height at Tx start	0.661	0.181	3.659	0.001
MPH	0.320	0.103	3.089	0.003
PAH at Tx start	0.097	0.143	0.679	0.500
ΔBA-CA at start	-2.032	1.107	-1.835	0.072
GnRHa Tx duration	2.044	0.480	4.263	0.000

Younger CA, taller height at the start of treatment, taller MPH and longer duration of GnRHa treatment were significantly related to NFH. But the PAH at the start of treatment and the difference between BA and CA did not appear to be associated with NFH

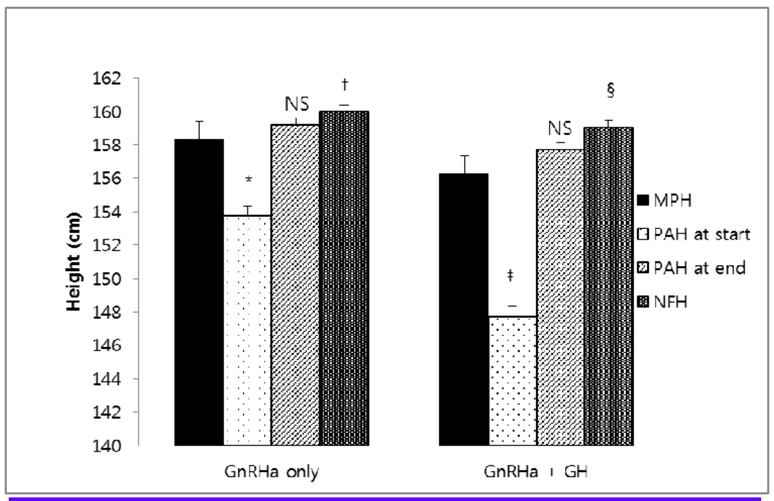


Figure 2. Comparison of MPH, PAH and NFH.
Compared with MPH, both groups showed shorter PAHs at start of therapy, but no difference at the end of therapy. NFH was significantly taller than MPH.

CONCLUSION

• GnRHa treatment could improve NFH in girls with CPP to at least a level similar to the MPH and could delay menarche so that it occurred close to the time it occurs in the general population. Combined GnRHa plus GH therapy, if used in CPP subjects with a short MPH, can improve NFH to a level similar to the average AH of the general population.

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