Improvement of final height in idiopathic central precocious puberty is associated with delay of bone maturation with GnRH agonist therapy under the age of 7 years

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INTRODUCTION AND OBJECTIVE

GnRH agonist (GnRHa) therapy with an onset before 6 years in girls with idiopathic central precocious precocious (iCPP) is beneficial to improve final height. However height benefit of GnRHa therapy with an onset after 6 years is controversial, since there is conflicting data. The aim of this study is to investigate the impact of age of onset of GnRHa therapy on final height in girls with iCPP, and to evaluate factors affecting height gain.

SUBJECT AND METHODS

Eighty-four girls with iCPP treated with GnRHa who reached final height were included. Patients were grouped as <6 yrs, 6-6.9 yrs, 7-7.9 yrs, ≥8 yrs according to age of onset of therapy. Final heights of the groups were compared with the heights of 18 girls with CPP who refused treatment. Height gain was defined as the difference between final height and predicted adult height (PAH) at the onset of therapy. The difference between bone ages at the end and beginning of therapy divided by the duration of therapy in years was used to calculate mean **Δ** bone age/year.

RESULTS

- The group treated before 8 years of age had significantly higher height gain compared to the untreated group (9.5±5.8 cm vs 5.7±4.0 cm) (p<0.001).

- The earlier the age of initiation of therapy, the higher the height gain (<6 yrs 13.3 ±6.1 cm, 6-6.9 yrs 9.8±5.8 cm, 7-7.9 yrs 6.6±4.9 cm) (p:<0.001).

- The earlier the age of initiation of therapy, the higher the height gain after the cessation of therapy (<6 yrs 10.2 ±6.1 cm, 6-6.9 yrs 7.1±5.9 cm, 7-7.9 yrs 5.6±3.9 cm, ≥8 yrs 4.0±2.9) (p<0.001).

- Pace of bone age advancement was reduced more effectively in those whose therapy started < 7 years of age (0.6±0.2 for <6 yrs of age, 0.6±0.2 for 6-6.9 yrs, 0.8±0.3 yrs for 7-7.9 yrs, 0.9±0.4 yrs for ≥8 yrs) (p<0.001).

- Untreated group and the group treated after 8 years of age had similar height gains (5.7±4.0 cm vs 5.9±4.2 cm) (p:0.852).

- The most important determinant of height gain was the age at onset of therapy, followed by target height SDS (standardized beta coefficients were -0.699 and 0.31,respectively) (r^2:0.626; p<0.001).

Table 1. Clinical and hormonal data at the diagnosis of CPP

	Total n=84	<6 year [a] n=14 (16.7%)	6-6.9 years [b] n=20 (23.8%)	7-7.9 years [c] n=20 (23.8%)	≥ 8 years [d] n=30 (35.7%)	Untreated [e] n=18	p value
Age at onset of puberty (yrs)	5.8±1.4	3.8 ± 1.0	5.4 ± 0.5	6.0 ± 0.5	6.9± 0.4	7.2 ± 0.8	<0.001[a,b,c,d,e,f,g,h,i,j]
Age at initiation of therapy- Chronological age (yrs)	7.1 ± 1.5	4.5 ± 1.1 (3-5.9)	6.5 ±0.4 (6.0-6.9)	7.5 ±0.4 (7.0-7.9)	8.3 ± 0.3 (8.0-9.0)	8.2±0.8	<0.001[a,b,c,d,e,f,g,o,p]
Bone age (BA) (yrs)	10.0± 0.9	8.4±0.9	9.8±0.2	10.1±0.5	10.7±0.4	10.4±0.8	<0.001[a,b,c,d,e,f,o]
BA advancement (BA-CA)(yrs)	2.8±0.8	3.9±0.9	3.3±0.7	2.6±0.5	2.4±0.2	2.2±0.7	<0.001[b,c,d,e,f,g,k]
Height for CA (cm)	129.4±8.2	116.8±6.7	127.9±4.2	130.4±4.6	133.8±5.6	135.6±6.2	<0.001[a,b,c,d,g,m,p]
Height SDS for CA	1.3±1.1	2.2±1.6	1.5±0.9	0.8±0.6	0.9±0.7	1.3±0.9	<0.001[a,b,c,d,e,f,i,q]
Height SDS for BA	-1.5±0.9	-2.0±1.2	-1.3±0.8	-1.4±0.8	-1.3±0.7	-1.0±0.8	0.048[a,c,d,n,p,q]
Basal LH (IU/L)	1.6±1.1	1.8 ±1.1	1.8 ±1.2	1.5±0.8	1.4± 0.6	1.2±0.8	0.426
Basal E2 (pg/ml)	37.9±18.4	68.6±31.6	38.2±16.4	30.8±12.6	28.2±14.8	26.8±12.8	<0.001[a,b,c,d,g,t,l,m]
Peak LH at GnRH (IU/L)	17.2 ±7.8	16.8 ±6.9	17.2 ±7.8	18.2±8.8	16.8 ±6.9	15.1±5.1	0.628
Duration of treatment (yrs)	3.9± 0.9	6.5 ±1.1	4.5 ±0.4	3.5 ±0.4	2.7 ±0.8		<0.001[a,b,c,e,t,o]
Age at menarche (years)	12.4±0.8					11.3±0.8	<0.001

Table 2. Auxological parameters of girls with idiopathic CPP

	Total treated (n:84)	<6 yrs (n:14)	6-6.9 yrs (n:20)	7-7.9 yrs (n:20)	≥ 8 yrs (n: 30)	Untreated (n:18)	p value
Final Height (cm)	158.3± 6.6	159.1±6.1	159.7±6.5	157.9±5.1	157.3±7.1	158.2± 7.3	0.224
Final height-SDS	-0.8± 1.1	-0.7± 1.0	-0.6±1.1	-0.9± 0.8	-1.0± 1.2	-0.8± 1.0	0.225
Target height (cm)	160.0± 5.3	161.2±4.2	162.3±4.5	158.9±4.1	158.7±3.8	159.3± 4.5	0.218
Target height-SDS	-0.5± 0.7	-0.3± 0.7	-0.2± 0.7	-0.7± 0.7	-0.7± 0.6	-0.6±0.7	0.220
PAH at diagnosis (PAH1) (cm)	150.1±5.2	145.8± 6.9	149.9± 4.9	151.3± 4.5	151.4± 4.4	152.3±4.7	0.024[b,c,d,k]
Height at the end of therapy (cm)	152.1±6.1	148.9±5.9	152.6±5.6	152.3±6.2	153.3±6.3		0.336
Height-SDS at the end of therapy	0.7±1.2	0.3±0.9	0.8±0.9	0.8±1.0	0.9±1.1		0.338
Bone age at the end of therapy (yrs)	12.7±0.7	12.1±0.5	12.4±0.7	12.9±0.8	13.1±0.8		<0.001[b,c,f,o]
Height-SDS for BA at end of therapy	-0.6±1.2	-0.6±0.9	-0.1±0.9	-0.6±1.0	-0.8±1.1		0.340
FH-TH (cm)	-1.7±4.7	-2.1±2.2	-2.6±4.5	-1.0±2.1	-1.4±3.5	-1.1±6.3	0.524
FH-PAH1 (cm)	8.2±5.3	13.3 ±6.1	9.8±5.8	6.6±4.9	5.9±4.2	5.7± 4.0	<0.001[a,b,c,d,e,f,g,r,s]
Final height-Height at end of therapy	6.2±4.8	10.2±6.1	7.1±5.9	5.6±3.9	4.0±2.9		<0.001[a,b,c,e,i,n]
Δ Bone Age/year	0.7±0.3	0.6±0.2	0.6±0.2	0.8±0.3	0.9±0.4		<0.001[l,m,o,p]

[a]p≤0.001 for <6 yrs vs 6-6.9 yrs, [b]p≤0.001 for <6 yrs vs 7-7.9 yrs, [c]p≤0.001 for <6 yrs vs ≥8 yrs, [d]p≤0.001 for <6 yrs vs untreated group, [e]p≤0.001 for 6-6.9 yrs vs 7-7.9 yrs, [f]p≤0.001 for 6-6.9 yrs vs ≥8 yrs, [g]p≤0.001 for 6-6.9 yrs vs untreated group, [h]p≤0.001 for 7-7.9 yrs vs ≥8 yrs, [i]p≤0.001 for 7-7.9 yrs vs untreated group, [j]p≤0.001 for ≥8 yrs vs untreated group, [k]p≤0.0125 for <6 yrs vs 6-6.9 yrs, [l]p≤0.0125 for <6 yrs vs 7-7.9 yrs, [m]p≤0.0125 for <6 yrs vs ≥8 yrs, [n]p≤0.0125 for <6 yrs vs untreated group, [o]p≤0.0125 for 6-6.9 years vs 7-7.9 years, [p]p≤0.0125 for 6-6.9 years vs ≥8 yrs, [q]p≤0.0125 for 6-6.9 yrs vs untreated group, [r]p≤0.0125 for 7-7.9 yrs vs ≥8 yrs, [s]p≤0.0125 for 7-7.9 yrs vs untreated group, [t]p≤0.0125 for ≥8 yrs vs untreated group

CONCLUSION

Treatment with GnRHa improve final height in girls with iCPP when started earlier than 8 years of age. This effect becomes more significant when treatment initiated earlier than 7 years of age due to more prominent reduction of bone age advancement. GnRHa treatment after 8 years of age dose not seem to improve final height.

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