Evaluation of final height in patients taking GnRH analogue: Should the age limit for precocious puberty be changed?

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BACKGROUND

The age limit for precocious puberty (PP) in girls is a topic that continues to be debated. As the age of onset of puberty in girls has gradually decreased, the studies that were performed in the last decades have advanced the opinion that the normal age limit for puberty should be reevaluated and the age limit for PP should be changed.

OBJECTIVES

The aim of the current study was to determine the diagnostic criteria to decide in whom it would be suitable and rational to start treatment among the girls whose breast development has initiated before age 8 and who were diagnosed with CPP according to the classical definition.

METHOD

The patients who were diagnosed with idiopathic central precocious puberty (CPP) were investigated in four groups as: patients in which GnRH treatment was initiated before age 6, between ages 6 and 7, between 7 and 8, and after age 8, and the final heights of these cases were evaluated. A fifth group was formed from patients who were diagnosed after age 7; however, they were not given treatment and were monitored for puberty progress, and the final heights of the group in which treatment was initiated and in which treatment was not initiated were compared. In all cases, the pubertal signs began before age 8, and there was advanced bone age, PAH at the beginning of treatment was significantly shorter than the target height, and the peak LH response in GnRH test was ≥ 5 mIU/ml. The cases who were not true CPP and who had only breast development were not included in the study.

RESULTS

All of the patients who underwent treatment reached a final height that was close to the target height, and while the final heights were taller than the predicted adult height (PAH) before treatment, the heights were shorter than the PAH at the end of treatment. It was observed that the cases in which treatment was initiated between ages 6 and 7 were similar to the cases in which treatment was initiated before age 6. A similar gain in height was achieved in these groups. It was also observed that the cases in which treatment was initiated between ages 7 and 8 were similar to the cases in which treatment was initiated after age 8 and they did not sufficiently benefit from treatment. While the height gain was 11.5± 1.6 cm in cases in which treatment began before age 7, it was 6.2± 1.8 cm in the group in which treatment began after age 7. The cases who were diagnosed and treated after age 7 and the cases in the same age group who were followed-up without treatment reached a final height close to the target height and the final heights of both groups were taller than the PAH at the time of diagnosis. The height gain without treatment was similar to the height gain with treatment in this age group (5.7± 2.0 cm vs 6.2±1.8 cm)

CONCLUSION

Of the cases who were diagnosed with CPP according to the classical definition, the number of cases diagnosed after age 7 was high and the height gains and final heights with or without treatment were similar. Thus, this suggested that, in fact, the puberty of these cases was normal and although the age of onset of puberty was earlier due to the secular trend, we unnecessarily investigated and treated these cases as we still used the classic age limit of 8 for the definition of PP. It is necessary to perform new epidemiological studies in population-based samples to determine the onset of puberty more precisely and to determine the age limits for the diagnosis of PP in different countries.

RESULTS

Table 1. Clinical and hormonal data at the initiation of GnRH analog therapy

	All treated Patients n=63	Patients aged <6 yr n=10	Patients aged 6-6.9 yrs n=15	Patients aged 7-7.9 yrs n=15	Patients aged ≥ 8 yrs n=23	p value
Age at onset of puberty yrs	5.9±1.3	3.9 ± 1.0	5.5 ± 0.5	6.0 ±0.5	7.0 ± 0.3	<0.001
Age at diagnosis (CA)	7.2 ± 1.4	4.6 ± 1.1	6.5 ±0.3	7.5 ±0.4	8.5 ± 0.5	<0.001
Bone age (BA) (yrs)	9.9± 0.9	8.3±0.9	9.8±0.2	10.0±0.5	10.7±0.4	<0.001
BA- CA (yrs)	2.7±0.7	3.7±0.5	3.3±0.4	2.5±0.3	2.2±0.2	<0.001
Height SDS for CA	1.8±0.9	2.7±1.7	2.2±0.8	1.4±0.8	1.3±0.8	<0.001
Height SDS for BA	-1.2±0.8	-2.0±1.2	-1.3±0.6	-1.0±0.7	-0.9±0.7	<0.001
Basal FSH (IU/L)	4.1±1.5	3.9 ±1.0	3.6± 1.1	4.5±1.5	4.2 ±1.9	0.305
Basal LH (IU/L)	1.5±0.8	1.6 ±0.9	1.7 ±1.0	1.4±0.7	1.3± 0.5	0.317
Basal E2 (pg/ml)	36.4±23.2	64.6±37.8	34.4±17.2	30.2±13.5	29.5 ±13.8	<0.001
Peak LH at GnRH (IU/L)	16.2 ±5.9	16.2 ±5.8	16.8 ±6.1	17.1 ±7.5	15.1 ±5.0	0.699
LH/FSH peaks ratio	1.1 ±0.1	1.1±0.1	1.1±0.1	1.2±0.1	1.2±0.1	<0.001
Duration of tx (yrs)	3.8± 1.4	6.4 ±0.9	4.5± 0.3	3.5 ±0.3	2.5 ±0.4	<0.001

Table 2. Comparison of cases taking GnRH analogue therapy according to age groups in terms of clinical, hormonal, and auxological data

	Treated patients aged < 7 years N=25 (groups 1 and 2)	Treated patients aged ≥ 7 years N=38 (groups 3 and 4)	p value
Age at onset of puberty (yrs)	4.7±1.1	6.6±0.6	<0.001
Age at diagnosis-(CA) (yrs)	5.7±1.1	8.1±0.6	<0.001
Bone age (BA) at diagnosis (yrs)	9.2±0.9	10.4±0.5	<0.001
BA-CA (yrs)	3.5±0.4	2.3±0.3	<0.001
Height SDS for CA at start of tx	2.4±1.3	1.4±0.8	<0.001
Height SDS for BA at start of tx	-1.6±0.8	-1.0±0.6	0.002
Basal FSH level (IU/L)	3.7±1.0	4.3±1.7	0.061
Basal LH level (IU/L)	1.7±1.0	1.3±0.6	0.107
Basal estradiol level (pg/ml)	46.4±30.7	29.8±13.5	0.008
Peak LH after GnRH (IU/L)	16.5±5.9	15.9±6.1	0.645
Peak LH/FSH	1.1 ±0.1	1.2± 0.1	<0.001
Duration of treatment (years)	5.3± 1.1	2.9± 0.6	<0.001
Total height gain during treatment (cm)	35.9±12.8	24.90±10.3	<0.001
Mean growth velocity during tx (cm/yr)	6.8±3.1	8.3±3.0	0.002
Final Height (cm)	159.3± 5.1	157.4± 5.2	0.115
Final height SDS	-0.5± 1.0	-0.8± 1.0	0.115
Target height (cm)	161.6± 4.1	158.5± 3.7	0.031
Target height SDS	-0.1± 0.7	-0.5± 0.6	0.031
PAH at diagnosis (PAH1) (cm)	147.8± 5.7	151.2± 4.2	0.007
Height at the end of tx (cm)	151.0±5.7	152.8±6.1	0.195
Height SDS at the end of tx	1.2±1.0	1.4±1.0	0.195
Bone age at the end of tx (yrs)	12.1±0.5	12.9±0.6	<0.001
Bone age advance at the end of tx	1.1±0.5	1.9±0.6	<0.001
Height SDS for bone age at the end of tx	0.3±0.5	-0.4±0.6	<0.001
PAH at the end of tx (PAH2) (cm)	162.7±5.9	161.4±5.6	0.359
Height gain after tx (cm)	8.3±4.1	4.6±2.5	<0.001
FH-TH (cm)	-2.3± 4.3	-1.1± 2.7	0.252
FH-PAH1 (cm)	11.5± 1.6	6.2± 1.8	<0.001
FH-PAH2 (cm)	-3.4±0.9	-4.0±1.5	0.009

Table 3. Comparison of cases who were diagnosed after age 7 and who were treated or untreated with GnRH analogue therapy

	Treated patients aged ≥ 7 years N=38 (groups 3 and 4)	Untreated patients aged ≥ 7 years N=18	p value
Age at the onset of puberty (yrs)	6.6±0.6	7.1 ±0.8	0.001
Age at diagnosis- (CA) (yrs)	8.2±0.6	8.1±0.8	0.482
Bone age (BA) at diagnosis (yrs)	10.4±0.5	10.1±0.9	0.051
BA-CA (yrs)	2.1±0.3	2.0±0.7	0.051
Height at diagnosis (cm)	133.4±4.2	134.6±5.1	0.141
Height SDS for CA at start of tx	1.4±0.8	1.4±1.0	0.894
Height SDS for BA at start of tx	-1.0±0.6	-0.6±0.8	0.757
Basal FSH level (IU/L)	4.3±1.7	4.1±1.9	0.574
Basal LH level (IU/L)	1.3±0.6	1.1±0.8	0.163
Basal estradiol level (pg/ml)	29.8±13.5	24.6±12.2	0.039
Peak LH after GnRH (IU/L)	15.9±6.1	12.9±4.9	0.005
Peak LH/FSH	1.2± 0.1	1.0±0.3	0.108
Final Height (cm)	157.4± 6.2	158.1± 7.1	0.916
Final height SDS	-0.8± 1.0	-0.9± 1.0	0.914
Target height (cm)	158.5± 3.7	159.1± 4.1	0.799
Target height SDS	-0.5± 0.6	-0.4±0.7	0.794
PAH at diagnosis (PAH1) (cm)	151.2± 4.2	152.3±4.7	0.711
FH-TH (cm)	-1.1± 2.7	-1.0±2.9	0.938
FH-PAH1 (cm)	6.2± 1.8	5.7± 2.0	0.282
Age at menarche (years)	12.3±0.8	11.2±0.7	<0.001

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