Different clinical courses of central precocious girls according to their age at presentation and treatment

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Purpose: The progressivity of central precocious puberty (CPP) seems to depend on the age at presentation. We evaluated the clinical courses of CPP girls according to their age at initiation of treatment.

Methods: One hundred thirty five girls with CPP diagnosed between Jan. 2003 and Dec. 2009 and regularly followed for more than one year were included. They were treated with gonadotropin-releasing hormone agonists (GnRHa) every four weeks. Subjects were divided into two groups based on whether they were treated before (Group I, N=20) or after seven years of age (Group II, N=115). We compared the anthropometric parameters, the predicted adult height (PAH), predicted treatment periods, and the laboratory findings of the two groups every six months.

Results: Out of 135 CPP patients, 123 were idiopathic and twelve had neurogenic problems. At the baseline, patients' average bone age (BA) was significantly older than chronologic age (CA) and PAH was significantly shorter than target height (TH). BA and CA were significantly older in group II, but the BA/CA ratio was significantly greater in group I. The average treatment period required to overcome the CA-BA difference was 4.64 yr (group I vs II; 7.98 yr vs 4.24 yr, $P < 0.01$), and the period needed to overcome PAH-TH difference was 2.49 yr (group I vs II; 4.37 yr vs 2.32 yr, $P < 0.01$).

Conclusion: Among the girls with CPP, the younger age group had more advanced BA than CA, and needed significantly longer treatment periods to overcome the BA-CA gap and PAH-TH gaps.

Keywords: Precocious puberty, Gonadotropin-releasing hormone

Introduction

Due to the growth plate's exquisite sensitivity to the actions of estrogens, auxological consequences of precocious puberty often precede the signs of sexual maturation and may result in the premature fusion of the growth plates, leading to adult short stature¹. The follow-up study from premature thelarche (defined by bone age [BA] advancement within 2 standard deviation of normal, normal growth rate and follicle-stimulating hormone [FSH]-predominant responsiveness to acute gonadotropin-releasing hormone stimulation) in 100 girls showed a 14% progression rate to central precocious puberty (CPP)². However, the course of sexual precocity is variable and there is a heterogeneity in the pattern of presentation, ranging from rapidly progressive to a slowly progressive puberty, or even complete regression of pubertal signs and no need for treatment^{3,4}. It is important to identify such an unsustained or slowly progressive type to prevent unnecessary treatment⁵. According to some investigations, a BA advance of less than 2 years⁶ or a lesser BA to height age ratio and lower estradiol levels⁷ could predict slower progression. In addition, clinical observation of boy's pubertal progression rate for at least six months could discriminate accelerated or slowly progressive puberty in CPP and even in the early puberty⁸. Therefore the progressivity of CPP seems to depend on the age of presentation. We investigated whether the clinical course of CPP differs

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according to the age of presentation and treatment.

Materials and methods

1. Population

Among the patients presenting with precocious puberty between January 2003 to December 2009, 135 girls with CPP who had been regularly followed up in the pediatric endocrinology unit for more than one year were assigned to this study. Informed consent was obtained from both them and their parents. The diagnostic criteria for CPP were breast development before eight years of age and stimulated luteinizing hormone (LH) levels of more than 5 IU/L⁹⁾. The numbers of patients according to their age at initiation of treatment were as follows: nine cases were less than six years, 11 cases were six to seven years, 61 cases were seven to eight years, and 54 cases were more than eight years old. The number of patients less than six years of age was so small that all subjects were simply divided into two groups depending on whether they had started treatment before (group I, n=20) or after seven years of age (group II, n=115). We used the initiation age of gonadotropin releasing hormone analog (GnRHa) treatment as a grouping criterion instead of breast development because the exact age of breast development was vague in most cases.

2. Methods

All of the CPP patients were evaluated for their BA and for basal serum values of insulin-like growth factor 1 (IGF-1), IGF binding protein-3 (IGFBP-3), and estradiol. The gonadal hypothalamic-pituitary axis was investigated by the basal and luteinizing hormone releasing hormone stimulated

measurement of plasma LH and FSH. We performed pelvic ultrasonography in all patients and brain magnetic resonance image in most of the patients. After patients were diagnosed with CPP, GnRHa was given as triptorelin or leuporelin depot forms of 30–120 µg/kg every four weeks. GnRHa has been prescribed until the patients' BA approaches 12 years.

Puberty ratings were made according to Tanner's scale¹⁰⁾. Final heights were predicted according to Bayley and Pinneau's method¹¹⁾ using BA, as assessed by Greulich and Pyle¹²⁾. Final predicted adult heights (PAHs) were expressed in relation to the mean normal adult height using standard deviation score (SDS). Target height (TH) was obtained from midparental height that was calculated by mean parental heights minus 6.5 cm.

Clinical courses and laboratory findings were evaluated every six months. We compared the anthropometric parameters, the calculated PAH and treatment periods, and the laboratory findings of the two groups.

3. Statistics

Statistical analyses were performed using SAS ver. 9.1 (SAS Institute, Cary, NC, USA). The results were expressed in mean±standard deviation. PAH and TH were changed into SDS. The anthropometric parameters and laboratory values before treatment were compared between group I and II using Student's t-test. After assuming the population from the sample using the Glimmix procedure, factors affecting the disappearance of the BA–CA, and PAH–TH differences were estimated. To estimate the periods and confidence intervals for these changes in relatively small samples, we used the bootstrapping method and a hierarchical general linear model, which was appropriate for the statistical analyses of repeated data measured at irregular

Table 1. Patients' auxological changes during treatment and follow-up periods

Variable	Before treatment	1st yr FU	2nd yr FU	3rd yr FU	4th yr FU
Tx/FU	135/135	135/135	54/58	16/25	3/5
Tx/FU (%)	100	100	93.1	64.0	60.0
CA (yr)	7.7±0.8 ^{a)}	8.8±0.9	9.7±0.9	10.5±1.1	10.4±1.7
BA (yr)	10.2±1.2 ^{a)}	10.6±1.1	11.1±1.0	11.7±1.1	11.7±1.4
BA/CA	1.32±0.14	1.22±0.11	1.14±0.12	1.11±0.09	1.13±0.09
BMI (kg/m ²)	17.0±2.2	17.9±2.6	18.9±2.9	19.9±3.6	21.0±4.5
HT (cm)	128.2±6.8	134.5±6.5	139.3±5.8	144.0±6.4	146.7±9.0
PAH (cm)	152.2±6.8 ^{b)}	155.9±6.1	157.1±4.9	159.6±5.4	163.2±3.3
ΔPAH		3.6±3.5	2.1±3.5	2.9±3.1	2.0±2.9
∫ ₀ ^{yr} ΔPAH		3.6±3.5	5.5±5.0	8.2±5.1	10.3±9.9
PAHSDS	-1.65±1.37	-0.90±1.21	-0.67±0.98	-0.15±1.07	0.56±0.66
TH (cm)			159.1±4.1 ^{b)}		
THSDS			-0.26±0.82		

Values are presented as mean±standard deviation.

FU, follow-up; Tx/FU, no. of patients with treatment/no. of patients with follow-up; CA, chronologic age; BA, bone age; BMI, body mass index; HT, height; PAH, predicted adult height; ΔPAH, increment of PAH between each FU year; ∫₀^{yr} ΔPAH, PAH increment after FU year; SDS, standard deviation score; TH, target height.

^{a)}P<0.0001 between BA and CA. ^{b)}P<0.0001 between PAH and TH.

intervals. The estimated periods were depicted as means and the corresponding intervals approximately by a 95% confidence interval (CI). $P < 0.05$ was considered statistically significant.

Results

1. Etiology of CPP

Out of 135 CPP patients, twelve patients (8.9%) showed neurogenic causes and the others were idiopathic (91.1%). Neurogenic causes were as follows: three hydrocephalus, two arachnoid cysts, one pineal cyst, one pituitary cyst, one partial empty sella, one cerebral palsy, one cortical atrophy, one Langerhans cell histiocytosis (LCH), and one tuberous sclerosis. Among the neurogenic causes, three cases were group I: one hydrocephalus, one pituitary cyst, and one tuberous sclerosis patient. The other nine cases were included in group II. The

percentages of cases with neurogenic causes included in both groups were statistically insignificant ($P=0.25$ by Fisher's exact test). Among the CPP patients with neurogenic causes, specific treatments had been completed in hydrocephalus, cerebral palsy, and LCH patients. Two neurogenic patients with cortical atrophy (group II) and tuberous sclerosis (group I) have been using antiepileptic drugs. The remaining causes were incidental findings; therefore, specific treatment was not required.

2. Auxological changes of CPP patients during GnRHa treatment and follow-up (Table 1)

At the beginning of treatment, patients' average CA was 7.7 ± 0.8 years, BA was 10.2 ± 1.2 years, the BA/CA ratio was 1.32 ± 0.14 , body mass index (BMI) was 17.0 ± 2.2 kg/m², TH was 159.1 ± 4.1 cm (-0.26 ± 0.82 SDS), and PAH was 152.2 ± 6.8 cm (-1.65 ± 1.37 SDS). The accumulated average increment of PAH was 5.5 cm over two years, 8.2 cm over three years, and 10.3 cm over four

Fig. 1. (A) The difference between BA (filled circle) and CA (open circle) was estimated to disappear at an average of 4.64 years of gonadotropin-releasing hormone agonist treatment. (B) The PAH (filled rectangle)–TH (dashed line) difference was estimated to disappear at an average of 2.49 years of treatment with increasing HT (open rectangle). (C) In addition, the PAHSDS (filled diamond)–HSDS (dashed line) difference became equal at 2.48 years of treatment, and the BA/CA ratio (filled triangle) approached to 1 in the 3rd and 4th years of treatment. BA, bone age; CA, chronologic age; PAH, predicted adult height; TH, target height; HT, height; PAHSDS, predicted adult height standard deviation score; HSDS, height standard deviation score; THSDS, target height standard deviation score; FU, follow-up.

years of treatment. The difference between BA and CA was statistically significant ($P < 0.0001$), and the difference between PAH and TH was also statistically significant ($P < 0.0001$). The age gap between CA and BA was estimated to disappear after an average of 4.64 years (95% CI, 3.74 to 5.54) of GnRHa treatment (Fig. 1A). An older age at the start of treatment ($P < 0.05$) and a longer duration of treatment ($P < 0.0001$) were factors influencing the disappearance of the BA–CA gap. The height gap between PAH and TH was estimated to disappear after an average of 2.49 years (95% CI, 1.96 to 3.01) of GnRHa treatment (Fig. 1B). For the PAH–TH gap, patients' age at the start of treatment showed no significant influence, but the treatment duration did ($P < 0.0001$). Likewise, after an average of 2.48 years of treatment (95% CI, 1.96 to 3.00), the difference between PAHSDS and THSDS was estimated to be insignificant

(Fig. 1C); the age at start of treatment had no influence, but the treatment duration did ($P < 0.0001$). The BA/CA ratio approached 1 between the 3rd and 4th years of treatment (Fig. 1C).

2. Comparison of the two groups' auxological changes (Table 2)

Before treatment, CA ($P < 0.0001$), BA ($P < 0.0001$), and the BA/CA ratio ($P < 0.05$) were statistically different between group I and group II, but other parameters such as HTSDS, THSDS, PAHSDS, IGF-1, IGFBP-3, basal LH and FSH, stimulated LH and FSH, and estradiol levels were not different (laboratory data not shown in the table).

The estimated period required to overcome the BA–CA difference was 7.98 years (95% CI, 3.88 to 12.07) for group I

Table 2. Patients' auxological changes during treatment and follow-up periods in groups I and II

	Before treatment		1st yr FU		2nd yr FU		3rd yr FU		4th yr FU	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
Tx/FU	20/20	115/115	19/20	115/115	8/8	46/50	5/5	11/20	3/3	0/2
Tx/FU (%)			95	100	100	92	100	55	100	0
CA (yr)	6.1±0.7 ^{a)}	8.0±0.5	7.1±0.8	9.0±0.5	8.0±1.0	10.0±0.5	8.6±1.0	11.0±0.5	9.3±1.2	12.0±0.6
BA (yr)	9.1±1.6 ^{a)}	10.4±1.0	9.5±1.6	10.8±0.9	10.4±1.9	11.2±0.7	10.5±1.8	12.0±0.6	11.2±1.7	12.5±0.0
BA/CA	1.48±0.19 ^{a)}	1.30±0.11	1.33±0.15	1.20±0.09	1.23±0.24	1.12±0.08	1.21±0.13	1.09±0.06	1.20±0.03	1.04±0.05
BMI (kg/m ²)	17.0±2.0	17.0±2.3	17.8±2.3	17.9±2.7	18.8±2.6	19.0±3.0	19.1±3.5	20.1±3.6	18.8±3.1	24.2±5.2
HT (cm)	121.0±7.1	129.5±5.9	128.1±6.6	135.5±5.9	132.4±7.8	140.3±4.7	134.7±7.1	146.3±3.5	141.4±7.4	154.7±1.9
PAH (cm)	153.3±10.5	151.9±6.0	157.3±8.3	155.7±5.6	155.4±8.2	157.3±4.3	158.3±9.3	160.0±4.2	162.4±4.2	164.4±2.1
ΔPAH			2.9±4.7	3.7±3.2	0.8±3.3	2.2±3.5	2.5±3.1	3.0±3.1	2.5±3.7	1.3±1.9
∫ ₀ ^{yr} ΔPAH			2.9±4.7	3.7±3.2	4.2±5.9	5.7±4.9	8.2±6.8	8.2±4.8	11.7±12.5	8.4±8.4
PAHSDS	-1.38±2.11	-1.69±1.20	-0.62±1.65	-0.95±1.12	-1.01±1.64	-0.61±0.85	-0.42±1.85	-0.09±0.84	0.40±0.83	0.79±0.41
TH (cm)	161.3±0.18	158.7±4.1								
THSDS	0.18±0.73	-0.34±0.81								

FU, follow-up; Tx/FU, no. of patients with treatment/no. of patients with follow-up; CA, chronologic age; BA, bone age; BMI, body mass index; HT, height; PAH, predicted adult height; ΔPAH, increment of PAH between each FU year; ∫₀^{yr} ΔPAH, PAH increment after FU year; SDS, standard deviation score; TH, target height.

^{a)} $P < 0.05$ between groups I and II before treatment.

Fig. 2. The estimated disappearing period for the BA (filled circle)–CA (open circle) gap in group I (A: average, 7.98 years; 95% confidence interval [CI], 3.88 to 12.07) was significantly different ($P < 0.01$) from group II (B: average, 4.24 years; 95% CI, 3.74 to 4.73). BA, bone age; CA, chronologic age; FU, follow-up.

(Fig. 2A), and 4.24 years (95% CI, 3.74 to 4.73) for group II (Fig. 2B), showing a significant difference ($P < 0.01$). In other words, the younger age group required a longer period of treatment to eliminate the BA–CA difference. The PAH–TH difference was estimated to be absent after 4.37 years (95% CI, 0 to 12.58) of treatment for group I (Fig. 3A) and 2.32 years (95% CI, 1.48 to 3.16) for group II (Fig. 3B), also showing a significant difference ($P < 0.01$). PAHSDS was assumed to converge with THSDS at 4.37 years (95% CI, 0 to 12.58) of treatment for group I (Fig. 4A) and 2.31 years (95% CI 1.48 to 3.14) for group II (Fig. 4B), showing a statistically significant difference ($P < 0.01$). Therefore, the younger age group required a prolonged treatment period for PAH and PAHSDS to reach the same levels as TH and THSDS, respectively.

Discussion

In our investigation, CPP was associated with neurogenic causes in 8.9% of patients, and the remaining 91.1% were idiopathic. At the start of treatment, their CA was significantly different from BA, and also PAH was significantly different from TH. The estimated GnRHa treatment period needed to eliminate the BA–CA difference was 4.64 years. The height difference between TH and PAH was estimated to disappear after 2.49 years of treatment. The average increment of PAH for the first year of treatment was 3.6 cm. From the results of the comparison between the two groups that were classified by age at the start of treatment, the younger age group had a significantly higher BA/CA ratio, though both BA and CA in

Fig. 3. The estimated disappearing period for the PAH (filled rectangle)–TH (dashed line) difference in group I (A: average, 4.37 years; 95% confidence interval [CI], 0 to 12.58) was significantly different ($P < 0.01$) from group II (B: average, 2.32 years; 95% CI, 1.48 to 3.16) with increasing HT (open rectangle). PAH, predicted adult height; TH, target height; HT, height; FU, follow-up.

Fig. 4. The estimated disappearing period for the PAHSDS (filled diamond)–THSDS (dashed line) difference in group I (A: average, 4.37 years; 95% confidence interval [CI], 0 to 12.58) was significantly different ($P < 0.01$) from group II (B: average, 2.31 years; 95% CI, 1.48 to 3.14) with a BA/CA ratio (filled triangle) approaching 1. PAHSDS, predicted adult height standard deviation score; THSDS, target height standard deviation score; BA/CA, bone age/ chronologic age; FU, follow-up.

group I were significantly lower than in group II. The younger group required a significantly longer time to overcome the BA–CA and PAH–TH differences. The higher BA/CA ratio was thought to be one of the reasons why the longer treatment period was required in group I.

It is difficult to evaluate the effect of GnRHa on final height, because a randomized controlled study is impossible. Thus, indirect methods, such as PAH calculated using the Bayley-Pinneau method or comparing with historical controls, were used in most references.¹³⁾ Although PAH calculated using the Bayley-Pinneau method showed good correlation with final height, PAH tended to be taller than final height¹⁴⁾. Another problem is that the patients treated for CPP are a heterogeneous group, with varying ages of onset and progression of pubertal development and other factors influencing growth^{1,14)}.

Our study has several limitations. First, the results included patients who had CPP with neurogenic causes. Although the percentage of neurogenic cases in our study was more than 5% higher than that usually reported in the prior reports¹⁵⁾, the effect of our neurogenic cases on the clinical course might be small because antiepileptic drugs were required in only two cases. In addition, the percentages of patients in the two groups who had CPP with a neurogenic cause did not differ. The second problem was grouping. The number of patients in group I was smaller than the number of patients in group II, and the number of patients after the second year of follow-up became even smaller. All of the group I patients were treated in the 3rd and 4th years of follow-up, but only half of the group II patients were treated in the 3rd year, and none of the group II patients was treated in the 4th year of follow-up. Because the patients who were followed up and treated until the 3rd or 4th year would not represent the initial patients' characteristics, we evaluated the height gaining effect of GnRHa by dividing the patients into two groups. Third, we also used the Bayley-Pinneau method instead of final height data to calculate PAH, but comparing the yearly increment in PAH using the same method might be significant in a statistical sense.

In many reports, GnRHa treatment has either not proven to be effective in improving final height in slow progressive CPP¹⁶⁾ or the height outcome has not found to be uncompromised in untreated slowly progressive variants of CPP^{5,14,17)}. However, in girls with precocious puberty or even with early puberty, a PAH of < 155 cm before or during therapy, a PAH of > 155 cm with a dramatic decrease in predicted height over six-month follow-up period, and/or advanced and rapidly progressing breast development were considered useful parameters in deciding which patients to treat⁴⁾. In addition, Carel and Chaussain¹⁸⁾ showed a final height gain of 5.3 cm in younger and 4.5 cm in older girls by grouping them before or after the age of six years according to the first signs of puberty. Apparently, the statural improving effect of treating girls with borderline CPP (six to eight years) was significant, similar to our result. They also noted that final height gain had no correlation with the age at onset of puberty or age at initiation of treatment¹⁸⁾. Similarly, our results showed patients' age at the start of treatment had no influence

on the disappearance of the PAH–TH gap.

In conclusion, according to our finding that the younger age group required prolonged treatment to overcome the BA–CA and PAH–TH differences, the younger the age a precocious girl is, the more prolonged the clinical course and treatment period will be.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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