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Familial Precocious Puberty: Clinical characteristics and GnRH agonist treatment outcome.

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Introduction

Puberty is one of the most mysterious process occurring human beings until now. Though numerous attempts to clarify the physiology of puberty are on-going, still there is much to be resolved. Most cause of central precocious puberty is unknown and the occurrence is sporadic. But some patients have familial history of precocious puberty. Recently genetic role is emerged on the pubertal progression, kisspeptin and MKRN3 is widely accepted as causative factor of the central precocious puberty, in some family But it couldn't expain everything causing central precocious puberty, and access to genetic analysis is hard yet. In this study, we defined familial precocious puberty (FPP) as the existence of more than one affected member in the proband generation. The others are considered as sporadic precocious puberty (SPP). The clinical aspects of familial precocious puberty and gonadotropin releasing hormone (GnRH) agonist treatment outcome was investigated comparing with sporadic precocious puberty. Clinical factors associated with PAH were analyzed.

Methods

From 1st January 2007 to 30th September 2014, 76 siblings were diagnosed with central precocious puberty in Ajou University hospital. They are 38 family consisted with 46 sisters, 16 sister and brothers and 14 identical twin girls. Boys are excluded in this study. Total 68 girls with FPP were identified, out of them 30 patients with FPP (6 patients were siblings) completed the GnRH agonist treatment. Subjects with SPP haven't family history of precocious puberty, and an only daughter was excluded. 61 patients with SPP completed the treatment. Patients with systemic illness, endocrine, nutritional of chromosomal abnormalities were excluded. Auxological parameters and laboratory findings were estimated with retrospective chart review. And pedigree was determined and maternal age at menarche was obtained by medical record or phone call. All subject performed GnRH stimulation test. If a girl showed breast engorgement, elevated peak LH level on GnRH stimulation test (above 5 IU/ml) and advanced bone age, she was diagnosed with central precocious puberty. The response of GnRH agonist treatment was assessed by auxological parameter including predicted adult height (PAH). PAH was estimated by Bayley- Pinneau method.

Statistical analyses

Results are described as mean ± SD unless otherwise stated. Comparisons between and within groups were performed with t- test. After GnRH agonist, treatment response was analyzed in 30 patients with FPP and all SPP. Association of auxological parameters and PAH after GnRH agonist treatment was assessed by multiple regression analysis. To avoid duplication of parents' height, target height and maternal age at menarche in FPP group, which of 38 patients with FPP were included in this analysis.

Results

The clinical characteristics of the initial presentation at the outpatient clinic were showed in Table 1. The 30 girls with FPP completed GnRH agonist treatment. Of that, the 8 girls with FPP were identical twin and 4 girls with FPP were sisters. Auxological parameters at the pretreatment and the last visit of GnRH agonist treatmen(post-treatment) with GnRH agonist treatment was compared by paired t-test(Table 2). . After treatment, PAH was revealed above their target height in both groups. Between both groups, auxological paramenters at the initial presentation were similar. The treatment period was 3.12 ± 0.47(yr) in FPP group, 3.08 ± 0.68(yr) in SPP (p >0.05). Growth velocity was 5.38 ± 0.76(cm/yr) in FPP group and 5.24 ± 0.61(cm/yr) in SPP group (p>0.05). But, post-treatment age was younger in SPP group than FPP group (11.48 ± 0.52 and 11.76 ± 0.30 (yr) respectively, p< 0.05).

Table 1. Baseline auxological parameters at the presentation.

	FPP (n=68)	SPP (n= 61)	P
Age (yr)	8.28 ± 0.78	8.39 ± 0.61	0.353
Height (cm)	133.08 ± 6.38	133.43 ± 5.80	0.745
Ht SDS	1.08 ± 0.85	1.05 ± 0.88	0.830
BMI (kg/m2)	17.27 ± 2.46	17.52 ± 2.05	0.537
BMI SDS	0.22 ± 1.10	0.37 ± 0.85	0.413
Target Ht (cm) *	158.35 ± 3.39	160.00 ± 3.83	<0.05
BA (yr)	10.18 ± 0.92	10.44 ± 0.72	0.086
BA-CA (yr)	1.90 ± 0.55	2.04 ± 0.71	0.218
Tanner stage (pubic hair)	1.01 ± 0.12	1.02 ± 0.12	0.939
Tanner stage (breast)	2.40 ± 0.52	2.44 ± 0.67	0.666
LH peak (IU/mL)	13.66 ± 8.35	12.13 ± 10.25	0.355
FSH peak (IU/mL)	13.11 ± 5.41	12.36 ± 4.95	0.418
Father's Ht (cm) *	170.81 ± 4.68	172.64 ± 5.75	0.102
Mother's Ht(cm) *	158.90 ± 4.63	160.36 ± 4.91	0.146
Maternal age at menarche(yr)*	12.51 ± 1.29	12.95 ± 1.17	0.094

. *; Father's height, mother's height and target heights was assessed in 38 families in FPP group, it was not duplicated.

Table 2. The change of Auxological parameter in FPP groups

	FPP (n=30)			SPP (n=61)		
	Pre-treatment	Post-treatment	p	Pre-treatment	Post-treatment	p
Age(yr)	8.57 ± 0.35	11.76 ± 0.30	<0.000	8.39 ± 0.61	11.48 ± 0.52	<0.000
Height (cm)	135.31 ± 4.90	152.11 ± 4.74	<0.000	133.43 ± 5.80	149.54 ± 4.62	<0.000
Height SDS	1.15 ± 0.65	0.56 ± 0.74	<0.001	1.05 ± 0.88	0.43 ± 0.84	<0.000
BMI(kg/m^2)	17.42 ± 1.72	19.74 ± 2.46	<0.001	17.52 ± 2.05	19.68 ± 2.69	<0.000
BMI SDS	0.31 ± 0.77	0.35 ± 0.86	0.680	0.37 ±0.85	0.38 ± 0.88	0.819
BA-CA(yr)	1.91 ± 0.47	0.12 ± 0.32	<0.001	2.04 ± 0.71	0.36 ± 0.62	<0.000
PAH(cm)	157.92 ± 5.30	165.21 ± 5.02	<0.001	156.37 ± 6.23	163.00 ± 4.76	<0.000
PAH-TH (cm)	-0.73 ± 4.11	6.54 ± 3.92	<0.001	-3.62 ± 5.39	2.99 ± 4.23	<0.000

At the final treatment time, height at the last time was higher in FPP group than SPP group(152.11 ± 4.74 and 149.54 ± 4.62(cm), respectively, p < 0.05) and bone age advancement was significantly smaller in FPP group than SPP group(0.12 ± 0.32 and 0.36 ± 0.62(yr), respectively. p <0.05). Post-treatment predicted adult height of FPP group was significantly higher than that of SPP group (165.21 ± 5.02 and 163.00 ± 4.76 (cm) respectively, p< 0.005). PAH increment was higher in FPP group (7.28 ± 4.37 cm) than SPP group (6.62 ± 5.75 cm), there was no statistical significance (p>0.005).

Clinical factors associated with PAH after the GnRH agonist treatment was analyzed by multiple regression . Pretreatment age, height SDS and treatment period was positively correlated with PAH. The peak level of LH on GnRH stimulation test was negatively correlated with PAH. Subject group was not associating factor with PAH after GnRH agonist treatment.

Conclusion

Familial precocious puberty was characterized by significantly lower target height than sporadic precocious puberty. GnRH agonist treatment improve the growth outcome both patients with SPP and FPP.

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