Gonadotropin-Releasing Hormone Analog Treatment in Children with Congenital Adrenal Hyperplasia Complicated with Central Precocious Puberty

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BACKGROUND and AIM

In patients with congenital adrenal hyperplasia (CAH), final height may be compromised due to high levels of androgens. This condition is more prominent in patients incompatible with treatment or in undertreated patients. Increased adrenal androgen production causes an alteration in bone age with loss of growth potential. Moreover, central precocious puberty (CPP) might be seen in those patients as a result of stimulation of the hypothalamic-pituitary axis. Gonadotropin releasing hormone analogs (GnRHa) have been used effectively in treatment of CPP since many years. By consistent stimulation of gonadotrophic hormones, GnRHa provide inhibition of cyclic secretion of those hormones and prevent the progression of puberty. Our aim in this study was to investigate the effect of GnRHa treatment on growth in patients with CAH and CPP.

DESIGN

Ten patients (aged between 2.4-8.8 years) who had been followed in pediatric endocrinology clinic with a diagnosis of CAH and with signs of CPP were included in this observational study. Eight patients have simple virilizing (sv) CAH and two have salt wasting (sw) CAH. This is an ongoing observational study. Seven children underwent GnRH stimulation test. Stimulated LH levels >5 mIU/mL were accepted as pubertal. Pelvic ultrasonography was performed in patients with 46,XX karyotype and surrenal ultrasonographic examination was performed in all patients. Pituitary and cranial magnetic resonance imaging (MRI) was performed in 8 patients with CPP. All patients underwent confirming mutational analysis of the *CYP21A2* gene. All patients were treated with hydrocortisone (14.3±2.5 mg/m^2). Mineralocorticoid treatment was added in two patients. GnRHa therapy (Leuprolide acetat) was used as 3.75 mg/q4wk and the dose had to be increased to 7.5 mg/ q4wk in two children. All CAH patients complicated with CPP examined in 3 months intervals. Bone ages, growth velocities (GV) and body mass indexes (BMI) of patients during treatment were evaluated.

RESULTS

On admission CA and BA were 6.18±2.1 years and 10.5±2 years, respectively (Table 1). Five children have 46,XX karyotype but one of them was reared as male (No 5). Mean follow-up was 4±1.8 years. Five children had homozygous mutation in *CYP21A2* gene (Table 2). Physical examination and ultrasonographic findings were given in Table 2. Hormonal results were given in Table 3. Mean duration was 0.82±0.54 years (0-2.08 years) between admission and the beginning of GnRHa-T. BA/CA was 1.93±0.6, 1.76±0.4 and 1.21±0.2 on admission, at beginning of GnRH-T and last visit, respectively (Table 1). A significant difference was found between BA/CA on admission and at last visit (p=0.002; t:4,322), and between mean BA/CA the beginning of GnRHa-T and at last visit (p=0.001; t:4,560) (Figure1). CA was significantly increased in girls than boys at the beginning of GnRHa-T (8.37±0.9 vs 5.2±1.5 years; p=0.032). GV was 5.96±2.2 cm, 6.98±2.9 cm and 4.77±2.8 cm at the end of first (GV1), second (GV2) and third years of the therapy, respectively. There is no statistical difference between GV1, GV2 and GV3. GV1 was negatively correlated with CA on admission (r:-0.680,p=0.030) and BA at the beginning of GnRHa-T (r:-0.668,p=0.035). GV2 was significantly inverse correlated between BA on admission (r:-0.882,p=0.002) and at the beginning of GnRHa-T(r:-0.884, p=0.002). GV2 also negatively correlated with height on admission (r:-0.707, p=0.033).

Table 1: Comparison of antrhropometric values of study population

	On admission	At the beginning of GnRHa therapy	At last visit on therapy
Chronologic age (CA), yr	6.18±2.1	6.78±1.8	10.1±2
Bone age (BA), yr	10.5±2	11.2±1.7	12.3±2.1
Height, cm	125±17	130.1±12	144±11
Predicted height, cm	152.6±10		159.1±9.7
BMI, kg/m^2	17±1.2	17±1.6	19±3.5^{a,b}
BMI-SDS,**	0.56(1.32)	1,09(1.52)	0.70 (1.49)

a: p=0.01 BMI vs Last BMI, b: p=0.004 GnRH-T BMI vs Last BMI
**: Median (IQR)

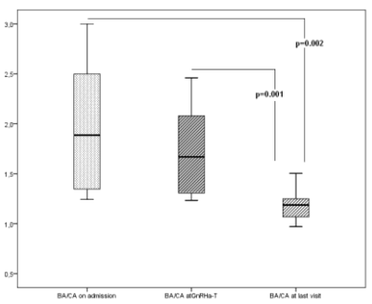

Figure: BA/CA at last visit was significantly different from admission BA/CA (p=0.002) and at GnRHa-Treatment (p=0.001).

Table 2: Clinical Findings of Study Population

Initials	Karyotype	Age (years)	Bone age (years)	Height (cm)	Predic-ted height (cm)	Mean parental height (cm)	BMI (kg/m^2)	Pubic hair stage	Breast stage	Penil length (cm)	Testicu-lar size (mL)	Uterus length (cm)	Right ovary (mL)	Left ovary (mL)	Adrenal hyper-trophy	CYP21 A2 Gene Analyses
CK	XX	7.08	8.8	130.5	167	160	19.67	III	I			18	1,80	,90	no	V282L, Homozygous mutation
CY	XX	8.80	11	141.5	160.8	158.5	16.28	III	II			36	6,50	2,70	no	No mutation
IS	XX	6.80	12	134.5	149.2	161.5	17.52	IV	I			15	1.07	1.35	no	P31L, Homozygous mutation
BNT	XX	7.80	10.5	127	148.3	153.5	15.50	III	I			35	1.19	0.86	no	V282L ,Homozygous mutation
RE*	XX	4.64	11.6	125	140.2	155.5	17.54	III	I	7.5*		40	0.51	0.48	yes	12G ,Homozygous mutation
YET	XY	4.00	12	115.5	142.7	167	18.37	III		8.5	4.00				no	No mutation
CK	XY	2,40	6	82	NA	176.5	16.36	I		11.5	4.00				yes	No mutation
BMK	XY	8.48	13	136.2	160.3	161	16.71	IV		10.0	10.00				yes	p.I173N, Homozygouts mutation
MC	XY	4.16	9	124	172.2	171	15.61	IV		11.0	4.00				no	No mutation
EC	XY	5.48	11	142	185.1	171	16.86	III		8.50	5.00				yes	No mutation

*: Reared as a male, NA: not available

Table 3: Hormonal results of patients

Initials	ACTH, pg/mL	Cortisol µg/dL	17-OHP, ng/mL	1,4AS, ng/mL	Testosterone , ng/mL	DHEAS, µg/dL	Renin, pg/mL	LH, mIU/mL basal	FSH, mIU/mL basal	LH, mIU/mL stimulated	FSH, mIU/mL stimulated	Estradiol, pg/mL basal
CK	334	17.4	23	2.72	.24	175	24.9	.15	1.32	NO	NO	40.1
CY	148	16.2	34.9	2.49	.81	660	44.6	1.17	6.63	17.39	16.41	36
IS	63	18.7	101	12.9	2.06	325	44	.65	3.02	18.90	11.20	47
BNT	37	15.84	18.8	2.91	.35	150	44.7	.91	.97	4.64	11.85	20
RE*	253	5.11	35	53	4.46	203	30	.10	1.22	NO	NO	28.6
YET	1250	3.53	55.7	5.2	129	38.8	270	.50	1.01	6.77	2.62	
CK	51	2.3	48	7.7	1.29	NA	539	.86	.57	5.83	2.34	
BMK	97	14.69	58.8	7.84	1.21	166	27.5	2.05	2.33	NO	NO	
MC	600	6.67	31	13.8	3.09	43	25.5	.69	1.89	9.27	4.57	
EC	1250	2.77	105	16.8	6.28	99	24.9	.10	.21	16.32	2.96	

NO: not obtained

CONCLUSION

In present study it was demonstrated that CPP might be seen at the time of diagnosis in patients with delayed treatment for CAH. Bone age was found considerably advanced at the time of diagnosis of CAH and this advancement has proceeded at the time of diagnosis of CPP. Yet treatment with GnRHa has been found to decrease the advancement of BA.
Furthermore, our results indicated that CAH patients with advanced BA at the time of diagnosis had decreased growth velocities. This finding was compatible with previous reports. Similarly, in CAH patients with advanced BA, growth velocity has been found decreased after GnRHa treatment. For that reason we suggest that patients with CAH who are complicated with CPP should be diagnosed early and treatment should be started immediately.