Congenital Adrenal Hyperplasia Complicated by Central Precocious Puberty: Linear Growth During Infancy and Treatment With Gonadotropin-Releasing Hormone Analog

Ashraf T. Soliman, Mohammed AlLamki, Issa AlSalmi, and Maurice Asfour

Some children with congenital adrenal hyperplasia (CAH) develop true precocious puberty with early maturation of the hypothalamic-pituitary-gonadal axis. We have seen six such children who had the diagnosis of CAH with late initiation of corticosteroid treatment and/or poor compliance who developed central precocious puberty (CPP). These patients were treated with standard-dose hydrocortisone and fludrocortisone. Administration of depot leuprorelin (3.75 mg subcutaneously every 28 days) for 2 years or longer was effective in arresting the manifestations of puberty, decelerating the pretreatment growth velocity ([GV] 10.8 ± 1.5 *v* 3.65 ± 0.95 cm/yr), increasing the predicted adult height ([PAHT] 147.5 ± 7.8 *v* 153.4 ± 8.3 cm), and decreasing the bone age to statural age ratio (1.26 ± 0.13 *v* 1.16 ± 0.09). Analysis of auxanological data during the first 2 years of life showed that linear growth was significantly accelerated and bone age was advanced in patients who developed CPP compared with 11 age-matched patients. It appears that proper glucocorticoid replacement to achieve adequate control of hyperandrogenemia during early life might prevent development of CPP in these patients. Gonadotropin-releasing hormone agonist (GnRHa) therapy can improve the final adult height, bringing it closer to that expected from the genetic potential.

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A VIRILIZING CONDITION that has been present for several years can, even when resolved, trigger true precocious puberty, presumably due to maturation of the hypothalamic-pituitary-gonadal axis. A good example of this is virilizing adrenal hyperplasia with late initiation of corticosteroid treatment and/or poor compliance.[1] Doses of glucocorticoid that permit mild chronic or intermittent hyperandrogenemia also seem to be associated with accelerated bone maturation and loss of height.[2] Gonadotropin-releasing hormone agonists (GnRHa) are capable of suppressing the hypophyseogonadal axis, and their use has completely modified the outcome of central precocious puberty (CPP).[3] These drugs, by permanently stimulating the gonadotrophe, induce a desensitization of the pituitary to hypothalamic luteinizing hormone (LH)-releasing hormone (LHRH).[4]

The aim of this study was to evaluate the efficiency of GnRHa in the treatment of children with virilizing congenital adrenal hyperplasia (CAH) and CPP.

PATIENTS AND METHODS

Six children (five girls and one boy) with CAH and CPP were included in the trial with the following criteria: clinical onset of pubertal development (breasts in girls and testicular enlargement in boys) before the age of 8 years in girls and 9 years in boys, pubertal response of LH to GnRH (peak > 10 IU/L),[5] plasma testosterone greater than 0.5 nmol/L in boys, uterine length greater than 36 mm by ultrasound examination in girls, and bone age greater than chronological age in both sexes. All children had a cranial computed tomographic scan at the time of diagnosis. Two patients (Af.A. and Ra.H.) had 11-hydroxylase deficiency, and the other four had 21-hydroxylase deficiency. Analysis of the history showed either a delayed initiation of treatment for CAH (Af.A. and Ka.M.) or prolonged periods of poor compliance to treatment.

Leuprolide acetate (3.75 mg per injection) was injected subcutaneously every 28 days, and the response of LH and follicle-stimulating hormone (FSH) to GnRH (100 $\mu m/m^2$) was measured at months 3, 12, and 24 after initiation of GnRHa therapy and 6 months after discontinuation of treatment. The dose of LHRH analog was increased to 7.5 mg per injection only in one girl, who had higher LH and FSH responses to GnRH than the accepted values for adequate suppression. Patients were receiving hydrocortisone and fludrocortisone replacement (17.5 to 22.5 $mg/m^2/d$) to keep circulating levels of 17-hydroxyprogesterone and renin (21-hydroxylase deficiency) or deoxycorticosterone (11-hydroxylase deficiency) at normal range.

All patients were treated for at least two years. They visited the clinic every 3 to 4 months for evaluation of auxanological, clinical, and biochemical parameters. The auxanological data included height, weight, height standard deviation score (HtSDS), and linear growth velocity (GV). Pubertal maturation (breasts and genitalia) was assessed according to the method of Marshall and Tanner.[6,7] Biochemical evaluation included determination of circulating 17-hydroxyprogesterone and renin or 11-deoxycorticosterone according to the enzyme defect, gonadal steroids, and serum electrolytes. Bone age was estimated yearly using the Atlas of Greulich and Pyle, and uterine length was evaluated by ultrasonography. The bone age to statural age ratio was calculated and recorded.

LH and FSH levels were measured using an immunoradiometric assay kit (Radium Pomezia, Rome, Italy). The mean intraassay and interassay coefficients of variation were 4.8% and 7.8%, respectively. Estradiol and total testosterone levels were measured by solid ^{125}I radioimmunoassay supplied by Diagnostic Products (Los Angeles, CA). The mean intraassay and interassay coefficients of variation were 4.6% and 7.2%, respectively, for estradiol and 4.1% and 8%, respectively, for testosterone.

To investigate the issue that hypersecretion of androgens with rapid growth and acceleration of skeletal maturation during the first 2 years of life might contribute to the early induction of CPP, the auxanological data of patients with CAH + CPP during the first 2 years of life were compared with those for 15 age-matched prepubertal patients with CAH who were under good clinical and biochemical control.

Results are presented as the mean ± SD. A paired Student *t* test was used to compare data before versus after treatment when data were normally distributed, and the Wilcoxon test was used when data were not normally distributed.

From the Departments of Pediatrics and Endocrinology, Royal Hospital, Muscat, Oman.

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Address reprint requests to Ashraf T. Soliman, MD, 3 Abdel Sattar Mansour St, Loran, Alexandria, Egypt.

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Table 1. Auxanological Data Before and After Treatment With GnRHa

		Pretreatment						End of Second Year				End of Treatment						
Patient Initials	Sex	PS	C Age (yr)	B Age (yr)	HtSDS1	GV1 (cm/yr)	PAHT (cm)	B Age (yr)	HtSDS2	GV2 (cm/yr)	PAHT (cm)	PS	C Age (yr)	B Age (yr)	HtSDS3	GV3 (cm/yr)	PAHT (cm)	MPHT (cm)
Af.A.	F	P2	7	12	1.02	10.2	141.4	13	0.49	4.2	145.5	P2	11	14	0.12	3.5	153.4	164.3
Ab.M.	F	P2	7.5	12	2.5	12.2	156.4	13	1.9	3.5	159.4	P2	10	13.25	1.85	3.8	160.5	167.2
Sa.A.	F	P2	8	12	0.6	8.2	142.8	12.5	0.35	3.4	147.6	P2	10	13	0.27	3.7	149.2	163.5
Pe.A.	F	P2	7.5	10.5	1.4	10.3	153.3	11.5	0.84	4.1	159.7	P2	9.5	11.5	0.84	4.1	159.7	169.5
Ra.H.	F	P2	5.5	12	2.3	12.3	136.5	12.5	1.6	3.5	143.8	P2	8.5	13.5	1.4	3.7	146.4	159.2
Ka.M.	M	P3	7	11.5	0.75	11.8	155	12.5	0.6	4.1	165.2	P3	10	13	0.8	6	168.9	172.3
Mean			7.1	11.7	1.42	10.8	147.4	12.6	0.96	3.87	153.4		9.75	13	0.87	3.8	156.1	166
SD			0.8	0.55	0.72	1.45	7.8	0.53	0.58	0.55	8.3		0.75	0.76	0.64	1.06	7.5	5.2

Abbreviations: C age, chronological age; B age, bone age; PS, pubertal stage (breasts in females and testicles in males).

RESULTS

Characteristics of the six patients are presented in Table 1. All patients had clinical signs of puberty before the age of 8 years in girls and 9 years in boys; the mean age at initiation of treatment was 7.1 ± 0.8 years. All had a bone age at least 2.5 years greater than their chronological age. The bone age to statural age ratio was greater than 1 in all patients. Computed tomographic scan of the hypothalamic-pituitary area did not show any abnormality. All patients had an LH response to GnRH in the pubertal range (Table 2). Plasma testosterone concentration was elevated in the boy.

Basal and peak LH and FSH values declined to prepubertal levels in all patients at month 3 and remained suppressed at the end of the first and second years of therapy. Gonadotropin suppression was achieved when the peak LH level was less than 3 IU/L, the 50th percentile of the normal prepubertal LH response for children aged 3 to 8 years. None of the patients had local reaction at the injection site, and none required an increase of the GnRHa dose. Gonadal steroids declined significantly during therapy. We considered plasma testosterone less than 0.5 nmol/L and estradiol less than 70 pmol/L to be indicative of adequate suppression.

Clinical signs of pubertal development regressed (Af.A.) or were stabilized in all patients. Menses had occurred in one patient (Sa.A.) before treatment, but none of the girls had menses thereafter. Uterine length decreased from 47 ± 6 mm at study entry to 41 ± 8 mm at 24 months.

Growth velocity decreased significantly from 10.8 ± 1.5 cm/yr during the pretreatment year to 3.65 ± 0.95 and 3.87 ± 0.55 cm/yr during the first and second treatment years. The predicted adult height (PAHT), using the tables of Bayley and Pinneau, increased significantly from 147.4 ± 7.8 cm before treatment to 153.4 ± 8.3 cm after 2 years of treatment and 156.1 ± 7.5 cm at the end of treatment (2.75 ± 0.7 years). During the first 2 years of treatment, bone age increased from 11.7 ± 0.55 yr to 12.6 ± 0.53 yr, indicating deceleration of skeletal maturation. The bone age to statural age ratio decreased from 1.26 ± 0.13 to 1.16 ± 0.09 at the end of the second treatment year (Figs 1 to 3). However, despite the improvement with treatment, the PAHT of the patients (156.1 ± 7.5 cm) was still below the midparental height (MPHT) (166 ± 5.25 cm) and lower than the PAHT of 10 age-matched children (161 ± 5.5 cm) with CAH under good control (age, 10.2 ± 1.5 years; bone age, 11.2 ± 1.2 years; and MPHT, 167.5 ± 4.6 cm).

Six months after discontinuation of treatment, LH and FSH peak responses to GnRH stimulation and gonadal steroids increased to pubertal levels, indicating reversibility of the suppressive effect of GnRHa on the hypothalamic-pituitary-gonadal axis.

Table 3 presents auxanological data for age-matched patients with CAH with and without CPP. All patients were born at or near full term, with normal birth size. There was no difference in size among the two groups. During the first year, the group of patients who developed CPP later had significantly taller stature (length standard deviation score [LSDS], 3.77 ± 0.9 *v* −0.9 ± 0.57) and faster linear GV. Analysis of the history showed that two of six were not diagnosed (late diagnosis at 2 to 4 years) and four of six had poor compliance to treatment with markedly elevated 17-hydroxyprogesterone or 11-deoxycorticosterone. In the second year, they continued to be taller (LSDS, 2.79 ± 0.78 *v* −0.8 ± 0.75) than those with good control with significant acceleration of the bone age.

Table 2. Hormonal Data Before and After GnRHa Therapy

	Before Treatment						6 Months After Discontinuation of Therapy					
Patient Initials	LH (IU/L) Basal	Peak	FSH (IU/L) Basal	Peak	E2 (pmol/L)	T (nmol/L)	LH (IU/L) Basal	Peak	FSH (IU/L) Basal	Peak	E2 (pmol/L)	T (nmol/L)
Af.A.	0.9	13.1	6.4	10.1	183	ND	2.7	39	5.2	16.5	233	ND
Ab.M.	2	38	1.8	8.2	93	ND	3.5	42	2.8	9.2	182	ND
Sa.A.	2.7	73	5.1	14.6	64	ND	3.5	52	3.8	12.7	110	ND
Pe.A.	1.7	15.2	2.7	9.9	85	ND	2.7	21	5.9	16	89	ND
Ra.H.	1.2	15.8	3.3	8.3	111	ND	3.2	28	3.8	14	225	ND
Ka.M.	7.8	16	3	14	20	11.3	5.3	32	4.8	17.5	ND	22

Abbreviations: ND, not determined; E2, estradiol; T, testosterone.

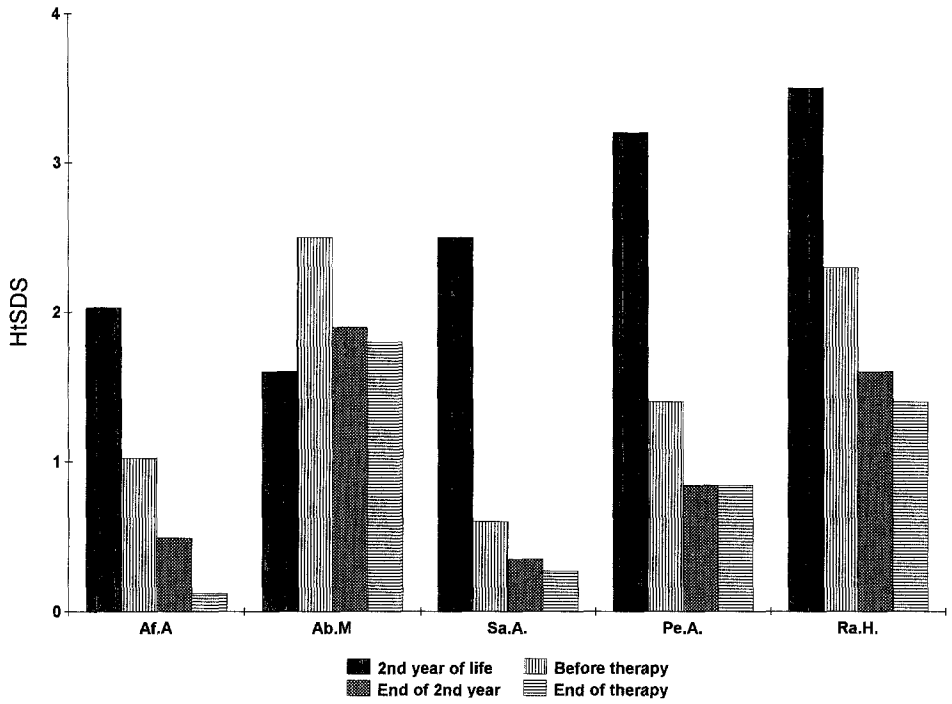

Fig 1. Height *z* scores before and after therapy.

DISCUSSION

Increased plasma concentrations of testosterone in boys and adrenal androgens in girls contribute to the adolescent growth spurt.[8,9] Hyperandrogenemia in CAH is present in early life, and to a variable extent postnatally depending on both the age at diagnosis and the degree of therapeutic control.[10,11] Inadequate control can lead to pseudoprecocious puberty in boys and true precocious puberty in both sexes.[12]

Although fetal adrenal steroidogenesis is established in early gestation, a boy with CAH rarely has signs of virilization at birth, despite plasma testosterone concentrations that are often within the normal adult male range.[12] The anabolic effect of fetal hyperandrogenemia is not significant on intrauterine growth. Newborn infants with virilizing CAH, including our patients (Table 3), usually have normal birth size. All six patients with CAH and CPP had a significant increase in growth and accelerated bone age during the first 2 years of life. These observations indicated that whereas linear fetal growth is not

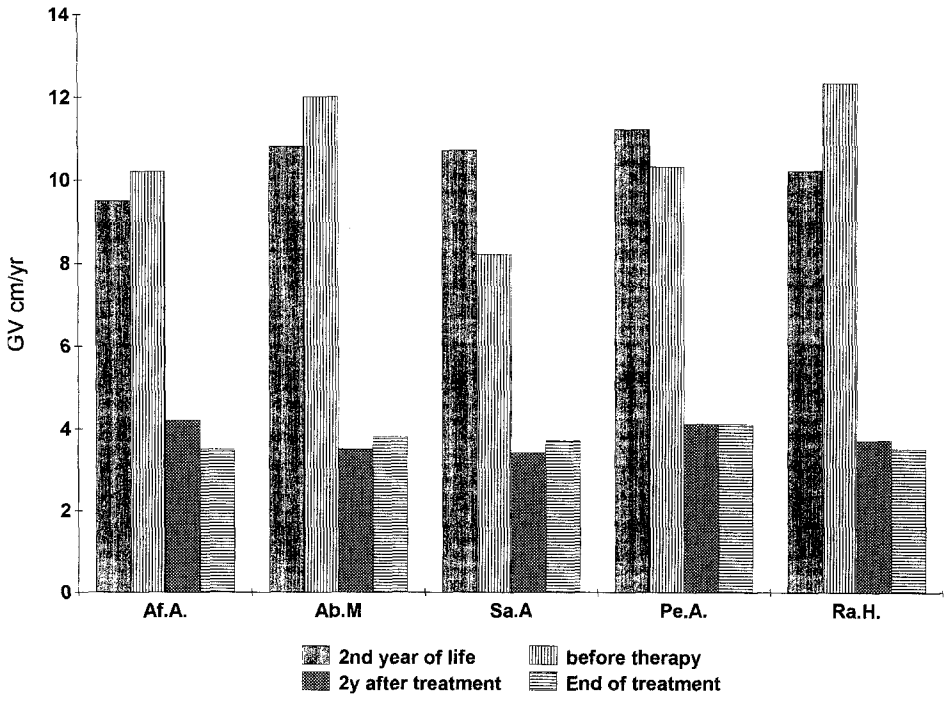

Fig 2. GV before and after therapy.

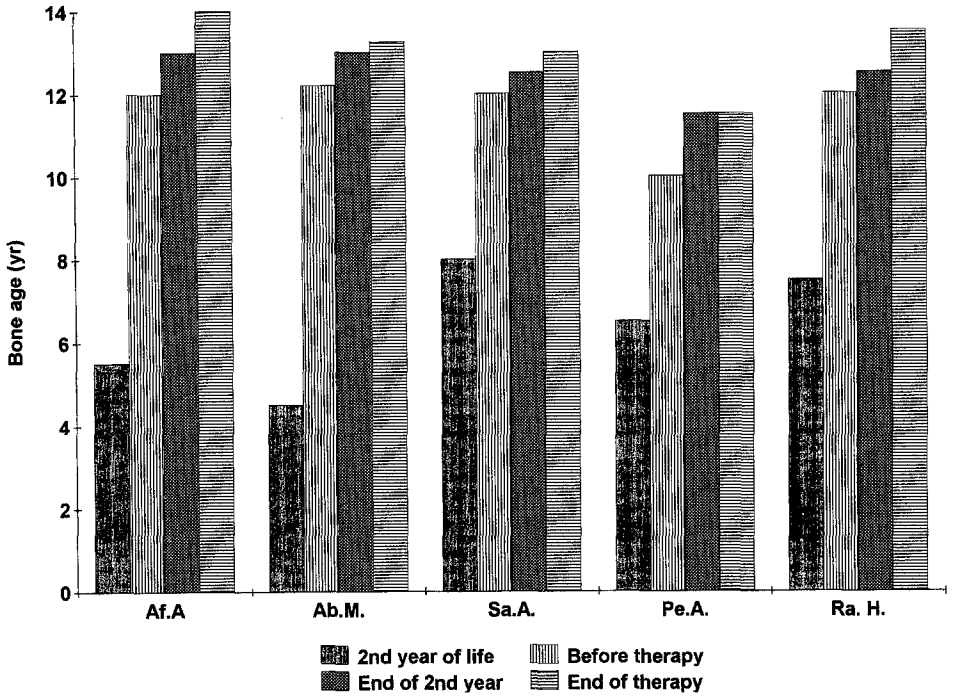

Fig 3. Bone age before and after therapy.

significantly affected by hyperandrogenemia, during early infancy growth is sensitive to androgens, with significant acceleration of skeletal maturation (Table 3). The effect of androgens on growth is probably a consequence of both direct and indirect actions. The direct action is mediated through stimulation of sulfation of proteoglycans in chondrocytes. Testosterone increases the width of the tibial growth plate and acts synergistically with growth hormone in this respect.[13-15] The indirect

Table 3. Auxanological Data of Patients With CAH With and Without CPP

	At Birth			First Year				Second Year				
Patient No.	Wt (kg)	L (cm)	BMI (kg/m²)	Wt (kg)	L (cm)	BMI (kg/m²)	GV (cm/yr)	Wt (kg)	L (cm)	BMI (kg/m²)	GV (cm/yr)	B Age (yr)
Patients with CAH + CPP												
1	3.4	51	13.1	12.2	84.5	17	33.5	17.1	94	19.4	9.5	5.5
2	3.3	51.5	12.7	11.5	81.5	17.3	30	13.4	92.3	15.7	10.8	4.5
3	3	49.3	12.3	12.5	85.3	17.17	36	15.1	96	16.4	10.7	8
4	3.2	50	12.8	11.8	87.3	15.5	37.3	12.3	98.5	12.7	11.2	6.5
5	3.7	53	13.2	12.8	89.3	16.05	36.3	14.3	99.5	14.4	10.2	7.5
6	3.6	52.5	13.1	10.5	84	21.5	31.5	12.5	94.5	13.9	10.5	4.5
Mean	3.36	51.2	12.86	11.88	85.3	16.3	34.1	13.7	95.5	15.4	10.5	6
SD	0.24	1.3	0.3	0.75	2.47	0.9	2.7	2.16	2.75	2.1	0.53	1.36
Patients with CAH (controls)												
1	3.2	50.5	12.5	10.1	74.7	18.1	24.2	10.9	82.5	16	7.8	1.5
2	2.9	50.2	11.5	8.1	67.6	17.7	17.4	9.6	77.3	16	9.7	1.5
3	3.1	49.3	12.75	7.9	69.6	16.3	20.3	10	81	15.25	11.4	2.5
4	3.2	50	12.8	8.4	71.5	16.4	21.5	11.3	84.5	15.8	13	2.5
5	2.8	49	11.7	8.1	71.5	15.8	22.5	9.4	80.3	14.6	8.8	2.5
6	2.7	47	12.2	7.6	72	14.6	25	12.5	85	17.3	13	3
7	3	51	11.5	7.1	70	14.4	19	11.2	84	15.8	14	2
8	2.6	49	10.8	7.8	70.8	15.56	21.8	9.9	82.9	14.4	12.1	1.5
9	3.1	50	12.4	8.6	74.2	15.6	24.2	10.3	86.3	13.8	8.7	2
10	3	48.8	12.5	7.6	72	14.7	23.2	11.7	88.7	14.9	16.7	3
11	4.1	51	15.7	10.4	78.5	16.9	27.5	12	88.4	15.3	9.9	2
Mean	3.06	49.6	12.4	8.34	72	16	22.4	10.7	83.4	15.4	11.4	2.18
SD	0.37	1.11	1.2	0.98	2.8	1.16	2.7	0.98	3.2	0.9	2.56	0.5

Abbreviations: Wt, weight; L, length; BMI, body mass index.

effect is the result of increasing growth hormone secretion.[16,17] Adequate glucocorticoid replacement during this period of life appears important to inhibit androgen hypersecretion and prevent development of CPP. In concert with our view, Lim et al[18] reviewed 89 patients with CAH due to 21-hydroxylase deficiency managed over a period of 25 years and found an increased risk of true precocious puberty in those who presented after infancy. On the other hand, growth is extremely sensitive to exogenous steroids, and even a small amount of steroid given in excess of physiological requirements may be detrimental.[19] Nevertheless, the potential loss of height can be minimized by titration of the glucocorticoid dose on sensitive biochemical measures of therapeutic control to supplement the standard criteria of clinical control. Children who have poor compliance could be treated with intramuscular cortisone therapy, particularly during the first 2 to 3 years of age.

In our patients treated with leuprorelin, despite improvement of the PAHT, it was lower than the target height (MPHT) and lower than the PAHT for the control group (children with CAH taking adequate therapy). This could be explained by their advanced skeletal maturation before initiating leuprorelin therapy. Other studies showed that good hormonal control resulted in taller patients.[20,21] However, a diminished final adult height of patients with CAH might still be an inevitable consequence for many patients receiving conventional glucocorticoid treatment that might permit mild chronic or intermittent hyperandrogenemia, or from the direct growth-suppressing effect of excessive treatment with glucocorticoid.[2,10,11]

In this report, depot leuprorelin effectively suppressed the gonadal axis in all treated children with CPP complicating CAH. This form of therapy administered for at least 2 years in adjunct with hydrocortisone and fludrocortisone increased the PAHT of patients with CAH who had compromised linear growth due to advanced skeletal maturation. The treatment appears to be safe and effective.

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