Near-final height in patients with congenital adrenal hyperplasia treated with combined therapy using GH and GnRHa

Altura quase normal em pacientes com hiperplasia adrenal congênita tratados com a combinação de GH e GnRHa

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ABSTRACT

Introduction: Intrinsic limitations of glucocorticoid therapy in patients with congenital adrenal hyperplasia (CAH) determine frequent loss in final height. The association of secondary central precocious puberty and early epiphyseal fusion is also frequent. In these conditions, GnRHa treatment alone or in combination with GH has been indicated. **Objectives:** This is a retrospective study, describing the estatural findings of CAH patients with significant decrease in height prediction, who were submitted to combined GH plus GnRHa therapy up to near-final height. **Subjects and methods:** We studied 13 patients, eight females and five males, eight with the classical and five with the nonclassical form of the disorder. Treatment with hydrocortisone (10-20 mg/m^2/day) or prednisolone (3-6 mg/kg/day) was associated with GnRHa (3.75 mg/months) for 4.0 (1.5) years, and GH (0.05 mg/kg/day) for 3.6 (1.4) years. **Results:** Stature standard deviation score for bone age improved significantly after GH treatment, becoming similar to target height at the end of the second year of GH treatment. **Conclusion:** We conclude that combined GH plus GnRHa therapy can be useful in a subset of CAH patients with significant reduction of predicted final height associated with poor hormonal control and central precocious puberty. Arq Bras Endocrinol Metab. 2011;55(8):661-4

Keywords
GH; GnRHa; congenital adrenal hyperplasia; height; growth recovery

RESUMO

Introdução: As limitações intrínsecas da terapia com glicocorticoides em pacientes com hiperplasia adrenal congênita (HAC) frequentemente determinam menor altura final. Também é frequente a associação de puberdade precoce central secundária e fusão epifisária precoce. Nessas condições, tem sido indicado o tratamento com GnRHa sozinho ou em combinação com o GH. **Objetivos:** Este é um estudo retrospectivo que descreve os achados de altura em pacientes com HAC que apresentavam diminuição significativa na altura predita e que foram submetidos ao tratamento combinado de GH com GnRHa até a altura quase normal. **Sujeitos e métodos:** Estudamos 13 pacientes, oito do sexo feminino e cinco do sexo masculino, oito com a forma clássica e cinco com a forma não clássica da doença. O tratamento com hidrocortisona (10-20 mg/m^2/dia) ou prednisolona (3-6 mg/kg/day) foi associado com GnRHa (3,75 mg/meses) por 4,0 (1,5) anos, e GH (0,05 mg/kg/dia) por 3,6 (1,4) anos. **Resultados:** O escore de desvio-padrão da estatura para a idade óssea melhorou significativamente após o tratamento com GH, tornando-se similar à altura normal ao final do segundo ano desse tratamento. **Conclusão:** Concluímos que o tratamento de combinação com GH e GnRHa pode ser útil em um subgrupo de pacientes com HAC que apresentem redução significativa da altura final predita, associado com controle hormonal inadequado e puberdade central precoce. Arq Bras Endocrinol Metab. 2011;55(8):661-4

Descritores
GH; GnRHa; hiperplasia adrenal congênita; altura; recuperação estatural

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INTRODUCTION

Medical therapy of congenital adrenal hyperplasia (CAH) is still a challenge, specially regarding the preservation of adequate final height. Growth during treatment is characterized by alternating periods of hypercortisolism with growth retardation, and hyperandrogenism with growth acceleration. Both hypercortisolism and hyperandrogenism eventually determine height loss at the end of puberty (1,2).

Despite apparent well controlled follow-up, several patients present reduced final height when compared with the general population or paired with familial target height (TH). Some of them reach very short stature at the end of growth, bellow two standard deviations (SDS) from the average population height (3).

Different therapeutic protocols have been suggested to prevent height loss, including variations in glucocorticoid schedule or association of glucocorticoids with anti-androgen drugs and/or aromatase inhibitors. As a consequence of irregular suppression of androgens, secondary activation of the hypothalamic-pituitary-gonadal axis is frequent, and represents an additional factor negatively influencing final height (4,5). In these cases, pubertal blockage with gonadotropin-releasing hormone analogs (GnRHa) is added to steroid replacement therapy; their prolonged agonistic properties, when offered as depot preparations, determine long-acting effects with consequent tonic inhibition of the pituitary-gonadal axis. Unfortunately, as an isolated treatment, GnRHa is usually able to prevent the progression of height loss, but it is ineffective in recovering previous height reduction (6).

More recently, the treatment with human growth hormone (GH) has been demonstrated to be able to improve growth velocity and final height in this condition (7-9).

Therefore, the aim of our study was to analyze growth response and near-final height in patients with CAH under combined therapy with GH and GnRHa.

PATIENTS AND METHODS

We performed a retrospective analysis from September 1999 to November 2009. During this period, there were 13 CAH who received, in addition to steroid replacement, a combined therapy with GH and GnRHa for at least one year.

Clinical and hormonal data were obtained in distinct time points: first evaluation, in the start of GnRHa blockage, in the start of GH therapy, at the end of the first year of combined therapy (GH plus GnRHa), at the end of the second year of combined therapy, at GnRHa withdrawal, at GH withdrawal, and at near-final height. Recorded variables were: parental stature, patient stature and bone age. Height was expressed as standard deviation score for gender and age, both for chronological age (SDS-CA) and for bone age, as determined by Greulich-Pyle method (SDS-BA). SD scores were calculated against reference data from the US population (NCHS, 2000). Final height evaluation was also compared with target height.

Hormonal control of CAH was based on 17OHprogesterone, androstenedione and testosterone values, and considered extremely variable and intermediate in the long term follow-up.

Thirteen CAH patients were included, 8 with the classical (two salt-wasting form) and 5 with the non-classical form of 21OHase deficiency. Eight with karyotype 46,XX, and 5 patients 46,XY. One 46,XX patient was raised as a male, but all calculated SDS values data were based on female reference standards.

The diagnosis was established at a mean (SD) age of 4.6 (2.9) years, ranging from zero to 9.0 years. Only two cases were recognized in the neonatal period.

The therapy with glucocorticoids included hydrocortisone (10-20 mg/m^2/d; divided into three doses) or prednisolone (3-6 mg/m^2/d; divided into two doses). GnRHa was administered intramuscularly every 28 days at a dose of 3.75 mg, for a period of 4.0 (1.5) years, ranging from 2.1 – 6.2 years. GH was injected subcutaneously at a daily dose of 0.15 UI/kg/day (0.05 mg/kg/day), for a period of 3.6 (1.4) years, ranging from 1.0 – 6.3 years.

Statistical analyses were performed with SigmaStat for Windows version 3.5, SPSS. The analysis of the same variable in different time points was determined by repeated measures ANOVA. Each time point was compared to the final evaluation by paired t Test.

RESULTS

Mean (SD) of the data on chronological age and bone age advancement observed at each time point is shown in table 1. On the whole, we observed that diagnosis was established around 5 years of age, and represented a group of patients with delayed recognition of the disease. Consequently, significant advancement of bone age was already present at the time of diagnosis. Time lag

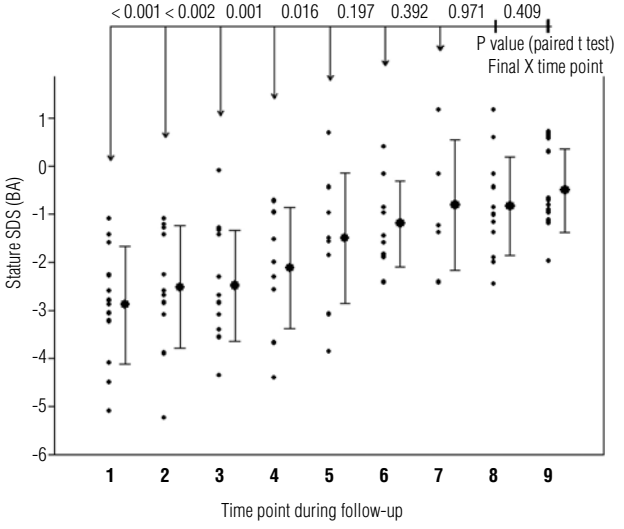
between gonadotropin suppression and GH initiation was around one year (0.5 – 2.0 years), during which no further bone age advancement was observed. At the end of combined GH plus GnRHa therapy, bone age advancement significantly decreased to 2 years, remaining around this value until the end of clinical evaluation.

Individual values of stature are shown in figure 1, expressed as standard deviation score (SDS) corrected for bone age. Each time point was compared with final height evaluation, showing a progressive increase in stature. From diagnosis to the end of the first year of combined therapy, stature remained significantly reduced in relation to the near-final height. When compared with final height evaluation, no significant difference in stature was observed from the end of the second year of combined therapy to the end of treatment. Final height evaluation was similar to target height.

Table 1. Chronological age and bone age advancement (years) in CAH patients

Time points	Chronological age (y)			* Bone age advancement (y)		
	Mean	SD	Range	Mean	SD	Range
Diagnosis	4.6	2.9	0-9.0	4.3	1,9	1.3-6.9
Start of GnRHa	7.2	1.8	4.9-10.0	4.2	1.9	1.0-6.7
Start of GH	8.1	1.9	5.2-12.0	4.4	2.2	1.0-7.9
GnRHa withdrawal	11.0	0.8	10.0-12.5	2.1	1.4	0.5-4.0
GH withdrawal	12.7	1.5	10.0-13.6	1.2	1.9	0-4.0
Final height	12.7	1.5	10.2-14.0	1.9	1.6	0-3.8

* Bone age advancement (y) = bone age (y) - chronological age (y).



1. First evaluation; 2. Start of GnRHa blockage; 3. Start of GH therapy; 4. First year of combined thepary (GH+GnRHa); 5. Second year of combined thepary (GH+GnRHa); 6. GnRHa withdrawal; 7. GH withdrawal; 8. Final height; 9. Target height.

Figure 1. Stature SDS calculated for bone age.

DISCUSSION

Replacement glucocorticoid therapy remains the standard treatment for CAH patients. However, growth suppressing effects of glucocorticoids, in addition to early epiphyseal fusion induced by elevated androgen levels eventually reduce growth potential and final height.

Few other reports addressed the benefits of combined therapy with GH and GnRHa. GH has been especially indicated in patients with reduction in predicted final height, usually associated with poor hormonal control and consequent early activation of the pituitary-gonadal axis, aggravating the acceleration of bone age.

Previous reports emphasized that early diagnosis and adequate intervention with glucocorticoids can prevent height loss and the need of GnRHa therapy.

Despite the fact that this is a retrospective study with relatively small number of patients, they where followed up to near-final height, and the results of combined GH plus GnRHa therapy, which are scarcely reported in the literature, were discussed.

This study described the addition of GH therapy to GnRHa treatment in a subset of CAH patients with poor or fair hormonal control, and secondary central precocious puberty. Some of the patients had delayed diagnosis, determining substantial bone age advancement and reduction of predicted final height. Our cohort, followed up to near-final height, showed a significant improvement in stature after GH therapy. Initial, isolated GnRHa treatment was able to prevent further height loss, but it was not sufficient to induce growth recovery. Addition of GH was able to increase height SDS for bone age, even in the first year of treatment, with significant growth recovery at the end of the second year of combined GH plus GnRHa therapy. At this time point, mean stature for bone age was similar to target height, remaining equivalent up to the end of follow-up.

We concluded that combined GH plus GnRHa therapy can be useful in a subset of CAH patients with significant reduction in predicted final height associated with poor hormonal control and central precocious puberty.

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