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Pubertal Development And Final Size of Children with Congenital Adrenal Hyperplasia

Aem Haddam[1],Ns Fedala*[2],L Ahmed Ali*[3]
Department Of Diabetology Bab El Oued Hospital Department Of Endocrinology , Bab El Oued Hospital*

Summary: *Congenital adrenal hyperplasia (CAH) are genetic diseases with a deficit of one of the enzymes of steroidogenesis (21 hydroxylase OH, 90%). Patients are often reach a reduced growth. The mean final height of these patients was 1.38 SD score lower than the population norm, and was lower than expected given parental height. both hyperandrogenism and hypercortisolism contribute to the observed short stature .*
Our objective in this study was to determine the distribution of achieved height in patients with classic CAH diagnosed at infancy or early childhood and treated with glucocorticoids.
Keywords: *Congenital adrenal hyperplasia, growth, short stature, hyperandrogenism and hypercortisolism*

I. Introduction

Congenital adrenal hyperplasia (HCS) is a genetic condition secondary to a deficiency in one of the enzymes of the steroidogenesis (21 OH hydroxylase, 90%). They often reach a reduced final height compared to their parentally determined target height. Different studies showed that the mean final height of these patients was 1.38 SD score lower than the population norm, and was lower than expected given parental height.[4] However, while there is general agreement on reduced final height in this population, there are still uncertainties related to certain factors affecting growth and optimal strategies to improve final height in CAH patients. Cependant both hyperandrogenism and hypercortisolism contribute to the observed short stature (1)(2) Our objective was to determine the distribution of achieved height in patients with classic CAH diagnosed at infancy or early childhood and treated with glucocorticoids.

Population,Methodology

This is a retrospective study of the final size of patients with congenital adrenal hyperplasia who have completed puberty. For each patient, we assessed age and size at diagnosis, target size, hydrocortisone doses, and mineralocorticoides taken, Use of height-enhancing drugs (lhrh analogues, biosynthetic growth hormone, Aromatases) size and age at the beginning and end of puberty, its course and androgen balance (17OH progeterone, testosterone)

II. Results

28 patients with congenital adrenal hyperplasia were identified. The majority were hydroxylase deficiency (n: 25, 89%). 10.7% (n: 3) had a 11 β hydroxylase deficiency. The sex ratio F / G was 21/7 The mean age at diagnosis and introduction of treatment was 8.5 ± 0.4 years (2-16) 20% of patients had an early puberty In the rest of the cases, a pubertal delay was observed with an average age of onset of puberty in girls at 14 ± 0.1 years, a mean age of 18 ± 1.3 ménarchie years, an early Middle Ages and the end of puberty in boys respectively 15 ± 1.4 years and 18.5 ± 0.4 years. All patients had polycystic ovarian dystrophy. 90% of patients had persistent hyperandrogenism due to glucorticosteroids (65%) and poor treatment compliance (35%) (Table I)

Table I: Mean ages of puberty

Parameter	Résults	Standards (Tanner)(3)(4)
Age of onset of puberty in girls (years)	14± 0,1 (13-16)	11
Age of onset of puberty in boys (years)	15±1,4 (14-17)	11,6
Age of the menarchy (years)	18 ± 1,3 (15-19)	13,5
Age of late puberty in girls (years)	17 ±0,5 (16-18,5)	16
Age of end of puberty in boys (years)	18,5 ±0,4	18

The mean final size was mediocre at 158.2 ± 2cm ;- 3.2 ± 0.2SDS / M (- 4.1, - 2.8) in boys and 150 ± 1.2 (140.6 - 1 54.8) ; -3.4 ± 0.6 among girls.

Mean final height of these patients was lower than expected given parental height - 3,5 ±1,02 (- 3,1 ; - 2,6) chez les garcons et - 4,2 ±0,4 (- 5,3 ; - 2,1) chez les filles (TableauII)

Table II: Average sizes of patients at diagnosis and during puberty

SIZE	**M (n =7)**	**F (n = 21)**
Average target size	170,6 ± 1,4 (163,4 – 175,6)	160,6 ± 2,7 (156,2 – 166,1)
Average size at first consultation X DS ± SDS (Extreme)	 - 3,1 ± 0,8 (- 4,5 ; - 2,5)	 - 4, 2 ± 1,2 (- 4,3 ; - 3,02)
Statural delay mean height / mid-parental height. à la 1ère consultation XDS ± SDS (Extrêmes)	 - 3,5 ± 1,02 (- 3,1 ; - 2,6)	 - 4,2 ± 0,4 (- 5,3 ; - 2,1)
Mean final height X cm ± SDS (Extrêmes)	 158,2 ± 2 (150,4 – 162,8)	 150 ± 1,2 (140,6 – 1 54,8)
Mean final height X DS ± SDS (Extrêmes)	 - 3,2 ± 0,2 (- 4,1 ; - 2,8)	 - 3,4 ± 0,6 (- 4,8 ; - 2,9)
Mean final height / mid-parental height. XDS ± SDS (Extrêmes)	 - 2,1 ± 1,1 (- 2,9 ; - 1,9)	 - 3,8 ± 1,03 (- 4,8 ; - 2,8)
Average total statural gain XDS ± SDS (Extrêmes)	 0,7 ± 0,5 (0,2 – 1,2)	 1,42± 1,1 (0,3 ; 2,4)

90% of patients had persistent hyperandrogenism due to glucocticoid (65%) and / or poor treatment compliance (35%): Mean testosterone 3.8 ± 0.6 nmol / L (3, 5-4.6) in girls and 20.5 ± 1.4 nmol / L (20-32) in boys; No patient with hydroxylase deficiency was substituted with mineralocorticoids (lack of available drug). All had Natremia at lower limit of normal: Mean natremia: 134 ±0,8 meq/l

III. Discussion

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. This condition has a worldwide incidence of approximately one in 15,000 births (1, 2). The most common form of CAH is attributable to mutations in CYP21A2, the gene encoding the adrenal steroid 21-hydroxylase enzyme (P450c21). This enzyme catalyzes conversion of 17-hydroxyprogesterone to 11-deoxycortisol, and progesterone to deoxycorticosterone, respective precursors for cortisol and aldosterone. The cortisol synthetic block leads to corticotropin stimulation of the adrenal cortex, with accumulation of cortisol precursors that are diverted to sex hormone biosynthesis (4).

Chronic hyperandrogenaemia during childhood results in rapid somatic growth with early epiphyseal fusion, ultimately compromising adult stature (5) (6). Additionally, central precocious puberty may develop in this population due to androgen activation of the hypothalamic-pituitary-gonadal axis, thus exacerbating premature epiphyseal fusion (7). In these children, with generally mild androgen excess, there was only small growth acceleration even in symptomatic patients. However, these untreated children exhibited pronounced bone age advancement (8). Higher doses of glucocorticoids in children with CAH may result in decreased linear growth, especially in early infancy and puberty, when growth velocity is at its peak Case of our patients .The negative impact of glucocorticoids on growth is dose dependent and occurs through multiple different mechanisms. Chronic glucocorticoid excess may suppress GH secretion by inducing enhancement of hypothalamic somatostatin release and may also suppress GH receptor and IGF-1 gene transcription. In addition, overtreatment with glucocorticoids suppresses the influence of the sex hormones on growth, resulting in a less profound growth spurt (9)

Authors recommended that the daily dose of hydrocortisone in patients with classical CAH should not exceed 17 mg/m^2 to maximize pubertal growth.(10) Mineralocorticoid (MC) replacement may allow management with lower doses of glucocorticoid in classic CAH patients. In addition, it was proven that all classic patients displayed variable degrees of aldosterone deficiency (11) The recent metaanalysis demonstrated better height outcome in the MC users compared with the non users (2)and the recent guidelines recommends that all classic CAH patients should receive fludrocortisone at diagnosis and during the first years of life. (11). The unavailability of the drug in our country did not allow us to use it

Type of glucocorticoid may affect final height. Use of potent longer-acting glucocorticoids such as prednisone or dexamethasone resulted in higher hydrocortisone equivalent doses and significantly reduced final height. (10° Therefore, It is recommended to use short-acting glucocorticoid for treatment of children with

CAH (10) . Early diagnosis and initiation of hydrocortisone therapy was associated with favourable stature outcome in individuals who presented before completion of puberty. Data related to the indications, efficacy and safety of height-enhancing drugs is limited. Antiandrogens, aromatase inhibitors, and growth hormone GH, alone or in combination with luteinizing hormone-releasing hormone LHRH analog, have been used in an attempt to improve the compromised height in CAH patients (14) (15). The 2010 Endocrine Society CAH Clinical Practice Guideline did not recommend the use of growth-enhancing drugs as standard treatment for CAH patients(11). However, these protocols should be considered in a subset of CAH patients with poor height prognosis due to poor hormonal control, advanced skeletal maturation, and central precocious puberty onset (14)(15) Further prospective, randomized, and carefully controlled studies would be helpful in determining whether the use of growth-promoting drugs increases adult height in patients with CAH.

With the application of systematic neonatal screening for congenital adrenal hyperplasia in our country allowing early diagnosis and treatment as well as compliance with optimal replacement therapy and close clinical and laboratory monitoring, particularly during infancy puberty, patients with CAH can reach a final height that is within their genetic potential with traditional medical treatment

IV. Conclusion

The delay in diagnosis in our patients resulted in a significant impact on statural growth and pubertal development. The final height of CAH patients treated with glucocorticoids is lower than the population norm and is lower than expected given parental height.

The introduction of systematic neonatal screening of HCS in our country and more effective management of the disease will improve the functional prognosis of patients

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