Editorial

Height outcome of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: Evidence from recent data

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Evidence derived from observational studies suggests that patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency often reach a reduced final height compared to their parentally determined target height.[1-3] A recent systematic review and meta-analysis of 35 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. Retrospective studies have shown that the adult height of treated patients is independent of the degree of hormonal control, which suggests that both hyperandrogenism and hypercortisolism contribute to the observed short stature.[3-5] Chronic hyperandrogenaemia during childhood results in rapid somatic growth with early epiphyseal fusion, ultimately compromising adult stature.[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] Interestingly, the excess of adrenal androgen secretion does not significantly affect growth and skeletal maturation during infancy (before 18 m of life), suggesting that growth prior to this time is insensitive to androgen exposure.[8] Moreover, the response to androgens is not only age dependent but also dose dependent, as showed by a recent study describing the height velocity of untreated symptomatic and asymptomatic children with the non-classical form of CAH. 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.[9] 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.[10] 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.[6]

Taking into account the relative androgen resistance of early infancy, the deleterious effects of glucocorticoids in early infancy and puberty, the doses of glucocorticoids prescribed during these two critical periods should be kept to a minimum and should not aim a too tight control of the disease.[6] A recent study 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[4] and the recent guidelines recommends that all classic CAH patients should receive fludrocortisone at diagnosis and during the first years of life.[12] Later, the need for

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ongoing MC treatment should be assessed individually.[12] In general, a statistically significant difference was seen for patients identified early versus late with better height outcomes in early diagnosed and early treated patients.[1] 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.[6] Therefore, as recommended by the paediatric consensus statement; short-acting glucocorticoid is routinely used for treatment of children with CAH.[11] Sex and severity of disease could represent additional height predictors. Males with the simple virilising form seem to have the poorest height prognosis, possibly due to late diagnosis and treatment, as well as an increased sensibility to aromatized estrogens from adrenal androgens compared to girls. Patients with non-classical CAH have a more favorable height prognosis than those with the classic form.[3] Adult height predictors in the non-classical form are controversial and may include age at diagnosis and at initiation of therapy and genotype (depending on the degree of severity: Mild/mild *vs* mild/severe).[13] Early diagnosis and initiation of hydrocortisone therapy was associated with favourable stature outcome in individuals who presented before completion of puberty.[13] Data related to the indications, efficacy and safety of height-enhancing drugs is limited.[12] 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] Interestingly, not all CAH patients require intervention to improve their final adult height. The 2010 Endocrine Society CAH Clinical Practice Guideline did not recommend the use of growth-enhancing drugs as standard treatment for CAH patients.[12] With extension of neonatal screening 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.[1] However, alternative 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.[2,6,14] 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.

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