

Editorial**Growth Management of Children and Adolescents with Cushing's Disease**

In this issue, Savage et al., summarize and discuss their data and those of the literature on the growth management of pediatric patients with Cushing's disease¹. Endogenous Cushing's syndrome is rare in all ages and children and adolescents represent about 10 percent of the total². The effect of hypercortisolism on growth is profound and proportional to both the severity and duration of the active illness. During active Cushing's disease, growth decelerates or completely stops, and bone age can be delayed, commensurate to the chronologic age or advanced, depending on the interplay of the delaying effect of hypercortisolism and the accelerating effect of adrenal androgen hypersecretion. It goes without saying that early diagnosis and therapy is key for final stature outcome.

The growth deceleration in active Cushing's syndrome is due to two major mechanisms: suppression of the spontaneous secretion of growth hormone (GH) and peripheral resistance of tissues to insulin-like growth factor-1 (IGF-1) and other growth factors^{3,4}. The molecular mechanism of the former is unknown. Acutely, administration of glucocorticoids is, in fact, stimulatory to GH secretion, yet chronic glucocorticoid excess is associated with varying degrees of GH deficiency. The molecular mechanism of the latter is better understood. The ligand-activated glucocorticoid receptor is a major reversible repressor of the transcription factor that mediates IGF-1 effects in the genome, the cjun-cfos heterodimer also called AP1 transcription factor. Correction of the hypercortisolism is expected to result in normalization of GH secretion, return of the tissue sensitivity to IGF-1 into the normal range and resumption of a normal or accelerated ("Catch-up") growth. And, generally, this is what happens when excess glucocorticoid administration is discontinued in children with exogenous Cushing's syndrome, a condition in which adrenal androgens are suppressed and the bone age is delayed.

Cushing's disease, however, is different. The growth-suppressive effect of cortisol excess usually overcomes the growth-promoting effect of adrenal androgens in postadrenarchal children with Cushing's disease, while the bone age is usually the same as the chronologic age in the majority of these children, and it can go in either direction in the rest². It is expected that the lower the adrenal androgens, the greater is the chance of having a delayed bone age. Also, in children with Cushing's disease, the insult to the pituitary gland during transsphenoidal surgery or radiation therapy frequently results in partial or complete GH deficiency, which may prevent resumption of a normal growth rate after remission of hypercortisolism. Interestingly, almost uniformly, children and adults with Cushing's disease have some degree of GH deficiency post-therapy. It thus behooves the endocrinologist to decide on the best course of therapy for obtaining optimal final height, such as GH therapy with or without pubertal arrest with GnRH analogs. With this therapeutic regimen the average final stature is compromised by less than one standard deviation unit, which may be acceptable for the majority of the patients⁵.

However, the management of the postpituitary therapy patient with Cushing's disease goes beyond obtaining a satisfactory final stature. There are additionally two other, potentially important, long-term problems: the recovery of a normal body composition and bone mineral density. In successfully treated children and adolescents, loss of weight, a decrease of BMI and an increase of bone mineral density into the normal range invariably take place. There may, however, be a residual effect on the body composition of these patients, including decreased muscle mass and an increase in total body or visceral fat mass that may be associated with residual insulin resistance and its sequelae.

This notion is substantiated by a pair of identical

twins, one of whom developed Cushing's disease at age 7-8 years but was diagnosed and successfully treated at age 15^{6,7}. The affected twin lost 21 cm of her final height, regained most of her bone mineral density and returned to a normal BMI of 24 at age 23 years. Nevertheless, her muscle mass and total fat mass, despite significant improvement, never returned to those of her genetically "identical" twin sister. These findings suggest that close monitoring and intervention, if necessary, is imperative in patients recovering from pituitary Cushing's disease. These conclusions extend beyond the pediatric age for Cushing's disease and syndrome and beyond the endogenous condition. Chronic exposure to glucocorticoids can have life-long effects⁸.

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