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REVIEW ARTICLE

Abnormal linear growth in paediatric adrenal diseases: Pathogenesis, prevalence and management

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Abstract

Abnormal adrenal function can interfere with linear growth, potentially causing either acceleration or impairment of growth in paediatric patients. These abnormalities can be caused by direct effects of adrenal hormones, particularly glucocorticoids and sex steroids, or be mediated by indirect mechanisms such as the disturbance of the growth hormone-insulin-like growth factor-1 axis and aromatization of androgens to oestrogens. The early diagnosis and optimal treatment of adrenal disorders can prevent or minimize growth disturbance and facilitate improved height gain. Mechanisms of growth disturbance in the following abnormal states will be discussed; hypercortisolaemia, hyperandrogenaemia and obesity. Prevalence and features of growth disturbance will be discussed in ACTH-dependent and ACTH-independent Cushing's syndrome, adrenocortical tumours, premature adrenarche, congenital adrenal hyperplasia and adrenal insufficiency disorders. Recommendations for management have been included.

KEYWORDS

adrenal disorders, adult height, growth plate, height, hyperandrogenism, hypercortisolaemia, paediatric

1 | INTRODUCTION

During childhood and adolescence, abnormal linear growth in disorders of the adrenal cortex can be related to either excess or deficiency of hormone secretion and may be key presenting features of primary adrenal pathology.[1,2] Several mechanisms can contribute to disturbance of normal height velocity, including hypercortisolaemia, affecting growth plate function, and its combination with increased sex steroid secretion, as in states of adrenal hyperplasia or adrenocortical tumours. Effects of cortisol excess and sex steroids on growth hormone (GH) secretion and production and action of IGF-1 can also impair growth, as can adrenal hormone deficiency, notably in salt-wasting states. Early diagnosis and skilled clinical management of abnormal adrenal hormone secretion can minimize the disturbance of growth and provide the best opportunity for the patient to reach a normal adult height. This review aims to discuss the pathogenesis and prevalence of abnormal growth in paediatric adrenal disorders and to discuss strategies for its prevention and normalization. The principal characteristics of growth disturbances and their mechanisms are summarized in Table 1.

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TABLE 1 Growth characteristics in paediatric adrenal diseases

Adrenal disease	Growth features	Mechanisms
Cushing's disease	Short stature, decreased growth velocity Compromise of postsurgical catch-up growth Virilization and abnormal pubertal growth	• Suppressive effects of GCs on growth plate chondrocyte development • GH deficiency related to hypercortisolaemia and obesity • Resistance to IGF-1 • Virilization due to adrenal androgens • GH deficiency postpituitary surgery and/or radiotherapy • Gonadotrophin deficiency due to hypercortisolaemia
Adrenocortical tumours	Virilization with advanced growth and skeletal maturation Gonadotrophin-dependent development after tumour excision	• Androgen to oestrogen aromatisation with chondrocyte stimulation and early ossification • Direct sex steroid effects on growth plate
Bilateral adrenal hyperplasia (PPNAD)	Short stature, decreased growth velocity Virilization	• Direct effects of GCs and adrenal sex steroids on growth plate
Premature adrenarche	Slight increased prepubertal growth Decreased pubertal growth spurt Normal adult height	• Adrenal androgen excess before 8 y in girls and 9 y in boys
Congenital adrenal hyperplasia	Possible infantile failure to thrive Advanced growth and skeletal maturation Slow growth Tendency to obesity Compromised adult height	• Cortisol and aldosterone deficiency • ACTH-drive to adrenal androgen excess • Supraphysiological doses of GC therapy • GC and sex steroid effects on growth plate
Autoimmune adrenal insufficiency	Normal or short stature	• Potential mineralocorticoid deficiency • Co-morbidities in APECED syndrome; compromising growth; thyroid dysfunction, malabsorption
Adrenoleukodystrophy	Normal growth	
Congenital adrenal hypoplasia	Failure to thrive	• Cortisol and mineralocorticoid deficiency • Hypogonadotrophic hypogonadism
Familial glucocorticoid deficiency	Tall stature in Type 1 Short stature in MCM4 mutations in Travelling families	• Suggested relationship with elevated ACTH levels • Genetic instability in MCM4 mutations
Triple A syndrome	Normal growth	

Abbreviations: GCs: glucocorticoids, GH: growth hormone, PPNAD: primary pigmented adrenocortical disease.

2 | PATHOGENESIS OF GROWTH DISTURBANCE RELATED TO ABNORMAL ADRENAL HORMONE SECRETION AND BODY COMPOSITION

2.1 | Hypercortisolaemia

Hypercortisolaemia in the paediatric age range can occur in association with ACTH-independent or ACTH-dependent Cushing's syndrome (CS) or excess administration of glucocorticoid (GC)-containing medications. The main ACTH-independent disorders are bilateral adrenal hyperplasia, typically primary pigmented nodular adrenocortical disease (PPNAD), and adrenocortical tumours. ACTH-dependent hypercortisolaemia occurs in Cushing's disease (CD), caused by excess ACTH secretion by a pituitary corticotroph adenoma or in the ectopic ACTH syndrome, which although well documented in children, is much less common than in adult endocrine practice. Iatrogenic hypercortisolaemia is seen in excessive administration of steroid-containing remedies such as tablets, skin cream, nasal sprays or nose drops and the therapeutic administration of high dose GCs for chronic illnesses.

Sustained exposure to GCs, as occurs in Cushing's syndrome where there is absence of the physiological cortisol circadian rhythm, or with supraphysiological long-term therapy, has severe effects on the growing skeleton causing impairment of linear growth. Although the clinical evidence of growth suppression related to hypercortisolaemia is not disputed, its molecular basis is highly complex and has been recently reviewed in detail by Hartman et al[3] Hypercortisolaemia suppresses both growth hormone (GH) and gonadotrophin secretion; however, it is principally at the peripheral end of the GH-IGF-1 axis that bone development is most affected. During postnatal life, long bones grow in length by endochondral ossification for which cartilaginous growth plates develop on both diaphyseal ends of the bones.[4] Chondrocytes, derived from limb mesenchyme during embryonic development, are located in three zones of the growth plate, the resting zone, the proliferative zone and the hypertrophic zone.[5,6]

Proliferating chondrocytes produce specific extracellular matrix (ECM) proteins that are crucial for the integrity of cartilage and for normal longitudinal growth; however, the interactions between the multitude of growth factors within the ECM is far from

understood.[4] When hypertrophic chondrocytes undergo apoptosis, osteoblasts invade the chondrocyte matrix lacuna, building a bone matrix.[7]

Both GH and IGF-1 signalling are required for physiological growth and can be inhibited by GCs at several levels. Glucocorticoid receptors have been identified in hypertrophic chondrocytes in the human growth plate, suggesting direct effects of GCs on growth plate function.[8] Exogenous steroid therapy, as demonstrated in studies in rats using dexamethasone, can inhibit the GH receptor, IGF-1 and IGF1R expression in primary chondrocytes, resulting in loss of paracrine actions.[9] Prolonged exposure to excess endogenous or exogenous GC concentrations will inhibit differentiation and proliferation of chondrocytes and suppress expression of antiapoptotic proteins which delays the progress of mineralization of new bone.[3] Growth plate vascularization, regulated by vascular endothelial growth factor (VEGF) and essential for endochondral ossification, is also disturbed by GCs as demonstrated in diverse in vitro and in vivo studies.[10] Hypercortisolaemia therefore disturbs the sensitive balance between chondrocyte differentiation, proliferation, apoptosis and vascularization in the growth plate thus disrupting linear growth.[3]

2.2 | Androgens

Hypersecretion of androgens is a feature in several adrenal disorders, notably congenital adrenal hyperplasia (CAH), PPNAD, adrenocortical tumours and to a lesser extent in Cushing's disease (CD). Excess circulating androgens promote growth indirectly by stimulating GH secretion through aromatization to oestrogens. Oestradiol, but not testosterone, stimulates GH secretion; therefore, aromatization of androgens is important for the stimulatory effect on pituitary GH release.[11] Aromatase, the enzyme that converts androgens to estrogens, is expressed in growth plate cartilage[12] and oestrogens stimulate chondrocyte development through two types of receptor (ER); ER-α and ER-β. Male patients with mutations of the ER-α gene or with aromatase deficiency have demonstrated that in both boys and girls oestrogen is the main determinant, together with GH, for puberty-associated linear growth and epiphyseal fusion. [4] High concentrations of oestrogen cause chondrocyte apoptosis leading to osteoblast invasion in the growth plate and advanced skeletal maturation and early epiphyseal fusion, a factor in influencing the decreased adult height in untreated hyperandrogenic states.

Androgen receptors have also been identified in the human growth plate,[13] and it is proposed that although testosterone per se does not mediate changes in hepatic gene expression of IGF-I, IGF-I receptor, IGFBP-1, IGFBP-3 or circulating IGF-I at the growth plate,[14] androgens do have stimulatory effects, independently of oestrogen action and influence local chondrocyte development.[15] In vitro studies have demonstrated this effect by nonaromatisable androgens.[14]

2.3 | Obesity

Obesity may also be present in adrenal disorders, as in CAH and CD, and has been shown to influence the dynamics of linear growth and the timing of puberty.[16] Childhood obesity is associated with normal or accelerated growth and children with simple obesity tend to be tall with advanced bone age.[17] Obese children have reduced GH secretion with normal IGF-1 levels, increased free IGF-1 levels and a tendency to hyperinsulinaemia, which in turn stimulates IGF-1 gene expression and increased action of the IGF-1 receptor.[18] In addition, suppression of IGFBP-1 leads to greater IGF-1 bioavailability which potentially stimulates growth. Leptin, a protein product of the obesity (*ob*) gene is secreted as a hormone mainly from white adipose tissue, serving as a signal for the brain of the body's energy stores.[17] In an animal study Leptin was shown to stimulate, in a dose-dependent manner, the width of the proliferative zone of the epiphyseal growth plate and to induce both proliferation and differentiation of chondrocytes.[19] Some of these effects on growing bone may be mediated by the IGF system through an increase in local IGF-1 receptor expression.[17]

3 | ACTH-DEPENDENT CUSHING'S SYNDROME

3.1 | Cushing's disease

Cushing's disease (CD) caused by an ACTH-secreting corticotroph adenoma is the most prevalent aetiology in paediatric CS over the age of 5 years, accounting for 50%-75% of cases.[2] Growth retardation is a well-recognized complication of CD being present in up to 80% of cases.[20,21] Short stature (height <–2.0 SD) was present in 37% of 52 patients with CS, including 45 with CD, and growth velocity when available was subnormal.[20] There was a striking contrast between height SDS, being almost always below the mean, and BMI SDS being consistently above it.[21] Height and BMI SDS values were compared with age-matched patients with simple obesity and showed a significant difference in the ratio of these two variables between the two groups,[22] height being increased in simple obesity and decreased in CD. Bone age in CD patients is usually delayed at diagnosis. In 17 CD subjects, bone age was delayed in 15 (mean delay 2.0 years; range 0.5 to 4.1) and correlated negatively with height SDS (r = −0.70; P < .01), duration of symptoms (r = −0.48; P = .05) and chronological age at diagnosis (r = −0.48; P = .05).[23] Children with CD have functional GH deficiency with reduced pulsatile GH secretion. Besides the direct consequences of GC excess, GH deficiency in CD patients might also be an indirect effect of obesity. Furthermore, a resistance to IGF-1 may contribute to growth failure through down-regulation of GH receptor function in the growth plate and an increase in circulating IGF-1 inhibitors.[9] Adrenal androgen excess that causes virilization in paediatric CD[24] may potentially promote advanced skeletal maturation[25] and accelerate epiphyseal closure via aromatization to oestrogens; however, in practice

TABLE 2 Height SDS at diagnosis and follow-up in paediatric Cushing's disease

Author and reference	Institution	Patients (N)	Mean/Median Age at diagnosis (y)	Mean Height SDS at diagnosis	Treatment	Mean/Median Follow-up interval Years (range)	Mean Height SDS at latest assessment
Acharya et al[26]	Medical College and KEM Hospital, Mumbai, India	48 (29 boys)	14.8 * (9-19)	−1.9 (−6.67 to 0.34)	TSS in 48, followed by: repeated TSS in 7; RT in 11; BAD in 4	4.1 (0 −10.7) (20 patients)	-1.84
Devoe et al[27]	University of California, San Francisco, USA	42 (17 boys)	13.1 * (6.5-18)	−1.8 (−3.5 to +0.3)	TSS in 42, followed by: Repeated TSS in 2; BAD in 4	7.2 (1.5-13.6) (7 patients)	-1.14 (−2.5 to 0.7)
Yordanova et al[29]	St. Bartholomew's and The Royal London Hospitals, London, UK	21 (13 boys)	12.1 * (5.7-17.8)	−1.5 (0.1 to −3.3)	TSS in 21 followed by repeated TSS + RT in 5; BAD in 1. hGH in 14	7.1 (2.7-17.3) (7 patients)	-0.99 (−2.84 to 0.46)

Note: Age expressed as Mean* or Median° and standard deviation or range.

Abbreviations: BAD: bilateral adrenalectomy; RT: radiotherapy; TSS: transsphenoidal surgery.

the growth-suppressive effects of hypercortisolaemia appear to dominate.

Mean height SDS values at diagnosis of CD are shown in Table 2.[26-30] At diagnosis, height SDS was <−2.0 in 40%-50% and <−1.5 in 58%-79% of patients[23,26,31] with growth more impaired in prepubertal compared with pubertal patients.[27,32,33] Height SDS was reported to be more severely reduced in Hispanic or African-American subjects compared with white non-Hispanic subjects (−1.6 ± 1.2 vs. −1.1 ± 1.1, $P < .05$).[34]

Despite remission of CD following successful treatment, catch-up growth can be variable and patients usually do not reach their genetic target height and frequently have adult short stature.[25,27-29,35] Adult height SDS values are shown in Table 2. No relationship between the duration of CD before diagnosis and adult height during remission was present in two large series of patients.[26,27] Reduced adult height may also be related to the onset of CD during puberty, giving insufficient time for full catch-up growth. Factors influencing catch-up growth include post-treatment GH deficiency, which has been clearly demonstrated after transsphenoidal pituitary surgery.[33] Pituitary radiotherapy for CD is a further cause of GH deficiency [36-38] which may persist for many years. Although no controlled data exist, we propose testing for GHD early during postsurgical remission, and treatment with GH may improve catch-up growth.[20] The addition of a GnRH analogue (GnRHa) to GH, also in the absence of controlled data, but extrapolating from management of other GH deficient patients[39] may increase long-term height gain by inducing deceleration of skeletal maturation.

4 | ACTH-INDEPENDENT CUSHING'S SYNDROME

4.1 | Primary nodular adrenal hyperplasia

Primary nodular adrenocortical hyperplasia (PNAH) is a rare cause of paediatric CS. Storr et al reported in a small but representative series of 6 patients with PNAH that at diagnosis 5/6 subjects had some degree of short stature together with weight gain and genital virilization. After treatment by bilateral adrenalectomy, 3/6 patients had catch-up growth with height velocities increasing from 3.0, 3.9 and 2.5 to 8.9, 8.3 and 9.0 cm/y, respectively.[40] Gourgari et al compared the growth of paediatric patients after curative surgical procedures in two forms of CS, namely CD (n = 18) and micronodular adrenal hyperplasia (n = 19).[28] Generally, patients with adrenal hyperplasia demonstrated better postoperative growth. The mean height SDS in the CD subjects before and 402 ± 27 days after pituitary surgery was −1.24 ± 1.14 and −0.91 ± 1.30, respectively, whereas the mean height SDS in the adrenal hyperplasia subjects before and 365 ± 87 days after bilateral adrenalectomy was −1.33 ± 1.64 and −0.62 ± 1.37, respectively. For patients in puberty Tanner stages 2 to 4 at surgery, the mean annual postoperative growth velocity was 10.5 ± 2.7cm/y in the adrenal hyperplasia group versus 7.4 ± 4.1cm/y in the CD group.[28]

4.2 | Adrenocortical tumours (ACT)

Childhood ACTs are rare and constitute approximately 0.2% of all paediatric malignancies, with the exception of in Southern Brazil, where the incidence of ACT is remarkably higher.[41] Clinical signs of autonomous adrenal hormone secretion are the most common presenting features, with virilization predominating but frequently accompanied by signs of oestrogen or cortisol hypersecretion. Pure cortisol-secreting ACTs only accounted for 5.5% of cases.[41] In a cohort of 28 patients with ACT, virilization and advanced growth were present in 60.7% at diagnosis.[42] Further reports showed that subjects with signs and symptoms of ACTs had above-average height SDS compared to age and gender-matched control subjects and height SDS of patients with virilization alone were significantly higher than in patients with mixed hormone hypersecretion.[43] In a series of 58 patients, 40% had heights >75th centile, and bone age was advanced by more than 1 year in 68% of the patients.[44]

While the increased growth velocity at diagnosis of ACT is established, little is known about growth after excision of the tumour and on adult height. Growth patterns after surgical removal of virilizing ACT in 9 girls, showed that 5 continued to grow rapidly for up to 18 months after surgery and subsequently had normal growth velocities.[45] Central precocious puberty is recognized as a potential complication after surgical removal of androgen-secreting ACTs[46] and in a retrospective analysis of 63 paediatric patients with virilizing ACTs, 58.7% developed early gonadotropin-dependent puberty, which was effectively treated by GnRH analogues, leading to normal adult height.[46] A clear message is that close clinical follow-up after removal of a virilizing ACT is crucial for early detection of activation of the hypothalamic-pituitary-gonadal axis and initiation of GnRH analogue therapy when clinically indicated.

5 | PREMATURE ADRENARCHE

Premature adrenarche (PA) is not an adrenal disorder, but rather an exaggeration of normal physiology. It is defined as increased levels of adrenal androgens before the age of 8 years in girls, and 9 years in boys with androgenic clinical signs such as body odour, acne, greasiness of hair and skin, and axillary or pubic hair.[47] Serum DHEA-S, androstenedione and testosterone concentrations are mildly elevated. It is important to exclude other pathologic causes of androgen excess, such as nonclassical CAH, familial male-limited precocious puberty, androgen-producing ACTs and exogenous androgen exposure.[48]

There are limited reports of adult height in girls with PA. A study of 34 girls showed that although the pubertal growth spurt was absent or reduced in 50% of the patients, final height was normal for parental heights.[49] Ghizzoni et al reported similar results in a study of 38 female patients, showing increased prepubertal growth with mean height at onset of puberty being 134.6 ± 1.2 cm compared with 129.9 ± 1.3 cm and 124.6 ± 0.9 cm in normal British and Italian girls, respectively. The advanced prepubertal growth was accompanied by a decrease of the pubertal growth spurt, with mean height velocity increase being 1.49 ± 0.25 cm/y compared with 2.28 ± 0.18 cm/y and 2.78 ± 0.12 cm/y in the normal British and Italian subjects and adult height being normal for target height.[50] The more pronounced the adrenarche and bone age advancement, the greater the acceleration of prepubertal growth, but adult height was normal.[51] In a prospective study of 30 PA and 42 control females assessed at a median age of 7.5 years, a normal outcome regarding adult height was reported, but with PA subjects having higher BMI persisting until puberty when females reached menarche at a median age of 11.5 years, approximately 1.5 years earlier than control subjects.[47]

6 | ADRENAL INSUFFICIENCY DISORDERS

Primary adrenal insufficiency (PAI) encompasses a group of disorders characterized by GC deficiency with or without associated mineralocorticoid (MC) deficiency.[52] Causes of PAI include impaired steroid biosynthesis in CAH, autoimmune dysregulation leading to Addison's disease or polyglandular syndrome (APS), abnormal accumulation of very long-chain fatty acids (VLCFA) in adrenoleukodystrophy (ALD), impairment of adrenal development in congenital adrenal hypoplasia (AHC), ACTH resistance in familial glucocorticoid deficiency (FGD) and triple A syndrome (Allgrove's syndrome). In children, CAH is the most common form of PAI, followed by APS and ALD, whereas AHC, FGD and triple A syndrome are extremely rare.[52,53] In children with PAI, growth disturbance may be present, since untreated cortisol deficiency may cause failure to thrive and growth retardation, whereas excessive GC replacement therapy may lead to growth suppression and reduced adult height.[53] Secondary adrenal insufficiency caused by hypothalamic or pituitary dysfunction is almost always associated with GH deficiency, which introduces a further compounding factor influencing linear growth.

6.1 | Autoimmune adrenal insufficiency

Autoimmune adrenalitis causes inflammatory destruction of the adrenal cortex. Both glucocorticoid and mineralocorticoid deficiencies may be present and the presentation may be insidious or acute depending on the degree of CG or MC deficiency. An acute presentation may be precipitated by a stressful event such as infection. There are few published studies of growth in autoimmune adrenalitis. A small study of 14 paediatric subjects reported normal growth in all subjects except in one girl who had positive ovarian thecal autoantibodies which impaired her pubertal development.[54] In MC deficiency states, the normalization of sodium balance with effective MC replacement has been shown to benefit linear growth and progression through puberty.[55]

Autoimmune polyglandular syndromes (APS) are characterized by the overlap of at least two autoimmune endocrinopathies and may be classified into four types.[56] Type 1 APS, also known as APECED due to the association of hypoparathyroidism, adrenal insufficiency,

mucocutaneous candidiasis and ungual dystrophy, has an estimated prevalence of 1:100.000, being the most frequent type in children.[52] Type 2 APS describes the association of adrenal insufficiency with type 1 diabetes mellitus or autoimmune thyroid diseases. In patients with APECED, hypogonadism related to positive steroid secreting cell autoantibodies, occurred more commonly in females which suppressed their pubertal development and growth.[57] Co-existing hypothyroidism and intestinal malabsorption can also potentially suppress linear growth.

6.2 | Adrenoleukodystrophy (ALD)

Adrenoleukodystrophy is a rare X-linked disorder with a prevalence of 1:17.000, characterized by adrenal insufficiency and neurological dysfunction.[58] Excessive accumulation of VLCFA in adrenocortical cells, oligodendrocytes and astrocytes leads to progressive development of PAI and myelopathies. A single case report describes a 23-year-old man who had GH deficiency diagnosed in childhood prior to the presentation of ALD and received successful GH replacement enabling normal catch-up growth.[59]

6.3 | Congenital adrenal hypoplasia (AHC)

Congenital adrenal hypoplasia is a rare X-linked disorder caused by deficiency of DAX1, encoded by the *NROB1* gene and characterized by impaired adrenal development during foetal life, with a prevalence estimated to be between 1:70.000 and 1:600.000 males.[60] Hypogonadotrophic hypogonadism accompanies the adrenal insufficiency. Normal birth length is described and presentation is usually during the neonatal period with no clear growth abnormalities documented during postnatal life. Appropriate GC and MC replacement is clearly important to maintain normal growth velocity.

6.4 | Familial glucocorticoid deficiency (FGD)

Familial glucocorticoid deficiency describes a rare autosomal recessive group of disorders, caused by resistance of the adrenal cortex to ACTH, resulting in cortisol deficiency. FGD is genetically heterogeneous, with mutations in the melanocortin receptor 2 (MC2R), (Type 1 FGD, 25% of cases), the melanocortin 2 receptor accessory protein (MRAP2) (Type 2 FGD, 20% of cases) and nicotinamide nucleotide transhydrogenase (NNT) (10% of cases). Mutations in the mini-chromosome maintenance complex component 4 (MCM4) are also included as a cause of FGD, as reported in the Irish Traveller population.[61]

Increased growth and tall stature are now well recognized in Type 1 FGD, as demonstrated in a study of 40 patients with Type 1 and 22 patients with Type 2 FGD. The Type 1 patients were significantly taller than Type 2 patients with mean heights of +1.76 SD and +0.12 SD, respectively.[62] It has been proposed that the tall stature might be related to elevated ACTH levels, since the introduction of GC replacement and the normalization of ACTH were associated with a decline in growth rate. Advanced growth continued in patients with persistently elevated ACTH levels or inadequate GC replacement.[63] In contrast, short stature has been reported in patients from Irish Traveller families carrying MCM4 mutations.[64] It has been suggested that their growth retardation may be related to genomic instability induced by MCM4 mutations, since other mutations related to the prereplicative complex, which is responsible for DNA synthesis in the S-phase, have been associated with short stature.[64]

6.5 | Triple A or Allgrove's syndrome (AS)

Triple A or Allgrove's syndrome (AS) is a form of ACTH unresponsiveness characterized by alacrima, adrenal insufficiency and achalasia and is caused by autosomal recessive mutations in the *AAAS* gene located on chromosome 12, encoding the 'ALacrima Achalasia aDrenal Insufficiency Neurologic disorder' (ALADIN) protein.[65] In healthy subjects, ALADIN is part of the nuclear pore complex, which plays a major role in intracellular communication between nucleus and cytoplasm. Reports are infrequent; however, AS does not seem to be associated with growth abnormalities.

6.6 | Congenital adrenal hyperplasia (CAH)

CAH encompasses a group of autosomal recessive disorders caused by mutations in genes encoding enzymes involved in cortisol biosynthesis.[1] Worldwide incidence, based on neonatal screening and national registries, ranges from 1:14 000 to 1:18 000 births. Ninety-five percent of CAH cases are due to mutations in *CYP21A2*, the gene encoding adrenal steroid 21-hydroxylase, which are characterized by varying degrees of impaired cortisol and aldosterone production associated with androgen excess. Conventionally, classical 21-hydroxylase deficiency is subclassified into salt-wasting and simple virilizing forms, based on the degree of aldosterone deficiency. In addition to these forms, which can be diagnosed at birth by neonatal screening, there is a milder 'nonclassical' form (NC-CAH) where up to 50% of enzyme activity can be retained. NC-CAH features varying degrees of postnatal androgen excess or may be asymptomatic (cryptic CAH). Treatment of classic CAH consists of life-long GC replacement, associated with MC replacement, particularly in the newborn and in infancy and childhood when indicated.[1] It is now well established that continuous GCs treatment with supraphysiological doses, aimed to reduce ACTH-driven androgen excess, can lead to impaired linear growth, resulting in reduced adult height.

Several pathogenetic mechanisms may disturb linear growth. Inadequate replacement of GCs will result in hyperandrogenism, leading to increased height velocity and advanced skeletal maturation, which if uncontrolled causes early epiphyseal fusion and subnormal adult height.[66] In 2010, a meta-analysis examining 35 studies found that mean adult height SDS achieved by CAH patients was

−1.38 (confidence interval −1.56 to −1.20) and the corrected height SDS, defined as final height SDS−mid-parental height SDS, was −1.03 (confidence interval −1.20 to −0.86). [67] The height deficit of −1.38 SDS is consistent with an approximate 10 cm deficit in adult height for a boy in the USA compared with the normal population.[67] The psychological effect of such a deficit is unknown. These findings of decreased adult height compared with the general population and below expected parental heights agree with data from the UK which showed that men and women had height SDS values adjusted for mid-parental target height of −2 and −1, respectively.[68]

6.7 | Glucocorticoid replacement in CAH

The recommended dose of hydrocortisone in the growing child with classical CAH is 10-15 mg/m^2 body surface area per day administered 3 times daily.[1] When doses exceeded 20 mg m^{-2} d^{-1} in infants and 15-17 mg m^{-2} d^{-1} in adolescents, there was loss of height SDS and reduced adult height.[1] In a persuasive study by Bonfig et al in 51 patients (27 females) with classical CAH, diagnosed by neonatal screening in Bavaria, Germany, the infants were treated with a low replacement dose of hydrocortisone 1 mg 3 times daily and fludrocortisone 0.05 mg 2 or 3 times daily.[69] The dose of hydrocortisone corresponded to 9-15 mg m^{-2} d^{-1}. Growth was meticulously monitored with determinations of 17- hydroxyprogesterone. During the first 3 years of life, height SDS decreased below average but at age 3 years height was normal for the genetic target and bone age was not advanced, despite the 17-hydroxyprogesterone level being elevated during infancy.[69] This study shows that low hydrocortisone dosing in infancy can preserve growth potential and because of a relative degree of androgen resistance during the first 6-12 months of life[70] suppression of 17-hydroxyprogesterone to normal levels is not necessary and is likely to cause overtreatment with GCs thereby decreasing long-term growth potential which may not be recovered.[1,71] The influence of growth during the first 2 years of life on adult height had been reported with infants who received a relatively high dose of hydrocortisone (19.6-28.2 mg m^{-2} d^{-1} showing a negative correlation between hydrocortisone dose and height at age 2 years.[72] It has been recommended that all patients with classic salt-wasting CAH should be treated with fludrocortisone and sodium chloride supplements in the newborn period and early infancy.[1] However, a recent large study has reported that infants with salt-wasting CAH who did not receive sodium chloride supplementation were at no disadvantage regarding linear growth or GC and MC replacement doses.[73]

Advanced bone age and GC replacement influence the quality of the pubertal growth spurt in classical CAH, which has a direct influence on adult height.[74,75] This phase of physiological rapid growth can easily be suppressed by overtreatment with GCs. Bonfig et al[74] reported that in a logistic regression model, a significant correlation existed between hydrocortisone dosage and adult height with the positive predictive value for short stature increasing to above 60% when daily hydrocortisone dosage exceeded 17 mg/m^2. In a second study, also using a regression model, hydrocortisone dose was negatively associated with predicted adult height, with each mg hydrocortisone/m^2/d during the growth period predicting a 0.37 cm decrease in adult height.[76]

Although growth dynamics are improving with a more personalized management approach using lower doses of hydrocortisone replacement, the subtle balance between suppressing excess androgens and providing physiological CG and MC replacement remains a major challenge to paediatric endocrinologists.[66] Infancy and puberty have been clearly identified as periods when overtreatment with GCs can be detrimental to growth.[71] In NC-CAH, growth is reported to vary between normal[77] or significantly advanced in some patients.[78] Early age of diagnosis and onset of treatment and the nature of the mutation dictating the degrees of cortisol deficiency and androgen excess are influencing factors.

7 | GROWTH SUPPRESSION DUE TO EXOGENOUS GLUCOCORTICOID ADMINISTRATION

Growth retardation is commonly experienced by children who receive long-term therapy with GCs.[79] Although chronic inflammatory disorders, such as arthritis and inflammatory bowel disease are relatively rare, the use of GC-containing medications, notably as inhaled GCs for commoner problems such as asthma, has enormously increased in recent years. The type and dose of GC preparation influence the degree of growth suppression, with even modest doses of prednisone (3 to 5 mg m^{-2} d^{-1}) or hydrocortisone (12 to 15 mg m^{-2} d^{-1}) causing growth suppression.[79] Alternate-day GC therapy reduces, but does not eliminate, the chances of growth delay, which may be inconsistent across a range of disorders. For example, children with nephrotic syndrome, ulcerative colitis and asthma were treated with more than 30 mg of prednisone every other day for 6 to 50 months without growth retardation.[80] However, alternate-day prednisone above 15 mg decreased growth velocity in many asthma patients, and resumption of normal growth was not observed with the switch from daily to alternate-day treatment.[81] The potential for catch-up growth following release from growth-inhibiting GC therapy will also depend on the disease activity of the underlying primary disorder.

A meta-analysis including studies of 810 GC-treated asthma patients, receiving oral or inhaled preparations, showed an overall tendency towards growth failure, particularly from oral prednisolone.[82] However, there were variations between different preparations, with inhaled beclomethasone being free from growth-suppressive effects.[82] Strategies for the reversal of GC-induced growth impairment in patients with GC-dependent primary disease include change to an alternative steroid preparation, for example oral to inhaled steroids, a reduction in GC dosage or a change of frequency of administration. In children with asthma, who are now largely treated with inhaled steroid preparations, the control of respiratory symptoms is more important than the potential growth-suppressive effects, which with skilled management can usually be limited to an adult height deficit of approximately 2.5 cm.[82] In GC-dependent nephrotic

syndrome, a study of 41 patients demonstrated that a daily prednisolone dose of <0.25 mg kg^{-1} d^{-1} did not negatively effect growth.[83]

7.1 | Secondary adrenal insufficiency

Among the adverse effects of long-term GC treatment, adrenal insufficiency secondary to suppression of the hypothalamic-pituitary-adrenal (HPA) axis is a cause for concern. Secondary adrenal suppression is related to the duration of therapy, the type and dosage of steroid used and the schedule of GC administration. After discontinuation of long-term GC therapy, secretory reserve of cortisol should be assessed using the short synacthen test (250 μg) (SST). In the event of cortisol deficiency, replacement should be given in a dose of 10-15 mg m^{-2} d^{-1} divided 3 times to allow recovery of the HPA axis, which may take many months or even years. Higher GC replacement doses must be given for episodes of trauma or sepsis, to prevent acute adrenal insufficiency. The extent of recovery can be assessed by omitting the evening hydrocortisone dose and measuring cortisol at 09:00 h the following morning. Ambulatory early morning serum cortisol is a guide to recovery of the HPA axis.[84] Evidence of endogenous cortisol secretion can prompt a reduction in the replacement regimen with further measurements of endogenous cortisol concentrations and SSTs as necessary.

8 | RECOMMENDATIONS FOR MANAGEMENT OF ABNORMAL LINEAR GROWTH

In Hypersecretion of androgens is a feature in several for clinical management are awareness of the disorders and their early diagnosis. Cushing's syndrome is rare in the paediatric age range and the diagnosis is frequently made after more than 2 years of symptoms.[20] However, the combination of four key clinical features should evoke the recognition of true pathology, namely growth failure, change in facial appearance, excessive virilization and weight gain.[20] Referral to a paediatric endocrinologist should then lead to investigation, diagnosis and appropriate therapy. Cooperation with an adult endocrinologist will yield major benefits in any child with suspected CS. Depending on the cause of CS, postoperative surveillance, whether postadrenalectomy or post-transsphenoidal pituitary surgery is essential. Both categories will require GC replacement which should be in physiological doses, using hydrocortisone rather than more growth-suppressive preparations such as prednisolone or dexamethasone.1 Following successful transsphenoidal surgery for CD, testing for hGH deficiency is recommended 3-months postoperatively followed by a low threshold for starting hGH replacement, if GH deficiency is confirmed. Provided that puberty is not at an advanced stage, the combination of hGH and a GnRH analogue to decelerate skeletal maturation is likely to increase adult height.[29,39] Catch-up growth following bilateral adrenalectomy for PPNAD was shown to be of good quality.[28]

Hyperandrogenic states also require early diagnosis to prevent excessive skeletal maturation. Following removal of a virilizing ACT, close monitoring of pubertal development is needed to recognize gonadotrophin-dependent characteristics and initiate their control with GnRH analogue therapy, if appropriate. Management of classical CAH presents arguably the greatest clinical challenge in order to balance GC replacement and control of androgen excess. New developments such as use of long-acting hydrocortisone preparations[85] and measurement of salivary adrenal-specific androgens to monitor control[86] are likely to be beneficial. Although most paediatric endocrinologists have experience of managing CAH, it is enormously beneficial for the child to see the same experienced specialist at each consultation visit. An individualized approach of expert assessment and fine-tuning of GC and MC replacement, together with regular auxological monitoring and biochemical analysis should avoid the need to resort to the expensive and somewhat experimental adjunctive treatments, such as GnRH analogues and human GH that have been proposed.[87]

9 | CONCLUSIONS

Hypo- or hyperfunction of the adrenal cortex during childhood can disturb linear growth causing either acceleration or reduction in height velocity. Both situations can lead to severe physical and psychological sequelae. There is increasing evidence of the importance of the early identification and prompt investigation and treatment of paediatric patients with adrenal disorders. Clinical skills remain paramount in the assessment of these patients and alignment with genetic, biochemical and pharmaceutical developments will add precision to their management, allowing growth and progress towards their genetically appropriate adult heights to be achieved.

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CONFLICT OF INTEREST

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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