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INVITED REVIEW

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Management aspects of congenital adrenal hyperplasia during adolescence and transition to adult care

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Abstract

The adolescent period is characterised by fundamental hormonal changes, which affect sex steroid production, cortisol metabolism and insulin sensitivity. These physiological changes have a significant impact on patients with congenital adrenal hyperplasia (CAH). An essential treatment aim across the lifespan in patients with CAH is to replace glucocorticoids sufficiently to avoid excess adrenal androgen production but equally to avoid cardiometabolic risks associated with excess glucocorticoid intake. The changes to the hormonal milieu at puberty, combined with poor adherence to medical therapy, often result in unsatisfactory control exacerbating androgen excess and increasing the risk of metabolic complications due to steroid over-replacement. With the physical and cognitive maturation of the adolescent with CAH, fertility issues and sexual function become a new focus of patient care in the paediatric clinic. This requires close surveillance for gonadal dysfunction, such as irregular periods/hirsutism or genital surgery-associated symptoms in girls and central hypogonadism or testicular adrenal rest tumours in boys. To ensure good health outcomes across the lifespan, the transition process from paediatric to adult care of patients with CAH must be planned carefully and early from the beginning of adolescence, spanning over many years into young adulthood. Its key aims are to empower the young person through education with full disclosure of their medical history, to ensure appropriate follow-up with experienced physicians and facilitate access to multispecialist teams addressing the complex needs of patients with CAH.

KEYWORDS
21-hydroxylase deficiency, androgens, cortisol, glucocorticoid, puberty

Chamila Balagamage and Amynta Arshad contributed equally to this study.

1 | INTRODUCTION

Congenital adrenal hyperplasia (CAH) comprises a set of autosomal-recessive errors of steroidogenesis affecting glucocorticoid (GC) biosynthesis in the adrenal cortex. This review focuses on the most common form of CAH caused by 21-hydroxylase deficiency (also: P450c21, CYP21A2), which causes about 95% of all CAH cases.[1,2] CYP21A2 catalyses the conversion of steroid precursors, progesterone and 17-hydroxyprogesterone (17OHP), into the mineralocorticoid and GC pathways, respectively. In CYP21A2 deficiency CAH, cortisol is reduced or absent, leading to increased negative-feedback-mediated pituitary corticotrophin (ACTH) drive resulting in chronic enlargement of the adrenal cortex, accumulation of steroid precursors, which are downstream converted into androgen pathways causing androgen excess. CAH is clinically categorised in a classic and a nonclassic form, which is molecularly explained by the degree of residual enzyme function.[1] The classic form with severely reduced enzyme activity typically manifests in the neonatal period and occurs in 1 in 12,000 to 1:18,000 based on CAH newborn screening data or national case registries.[1]

Excess androgen production causes virilisation of the external genitalia in 46,XX infants. If aldosterone production is impaired and the condition is unrecognised, the infant will suffer from severe salt-wasting adrenal crisis within the first weeks of life. Some degree of residual enzyme activity may be sufficient to ensure aldosterone production, but the child is still at risk of developing adrenal crisis in the so-called 'simple-virilising' form. Children with undetected or poorly managed classic CAH may, through chronic androgen exposure, develop precocious puberty with subsequent short stature. In the nonclassic form, where residual enzyme activity maintains sufficient cortisol and aldosterone production to prevent salt-wasting crisis, androgen excess symptoms become clinically evident and trigger healthcare attention during childhood, adolescence or even adulthood.

In classic CAH, 17OHP levels are typically exceeding 300 nmol/L (10,000 ng/L),[3] but nonclassic CAH (NCCAH) is suspected biochemically if a baseline early-morning or ACTH-stimulated 17OHP is raised above 30 nmol/l (1000 ng/dl).[2] Genetic analysis of the CYP21A2 gene confirms the diagnosis and is an important aid when the biochemical results are equivocal, or ACTH-stimulation testing cannot be performed accurately.[2]

A key therapeutic goal in classic CAH across the life-span is to restore the imbalanced steroid hormone equilibrium by replacing GCs and mineralocorticoids to avoid adrenal/salt-wasting crisis and reduce the degree of androgen excess due to cortisol deficiency. During childhood, the GC treatment of choice is divided doses of oral hydrocortisone reflecting circadian rhythm, combined with fludrocortisone and salt supplementation during infancy in the classic form. A focus during childhood and adolescence is to achieve adequate height outcomes.[2] Underreplacement of GCs may provoke excess adrenal androgen production with high childhood growth velocity, bone age advancement and reduced adult height (AH); over-replacement with GCs may cause stunted growth and weight gain, exacerbating the risk of cardiometabolic complications.[4]

The adolescent period poses significant challenges for the management of CAH.[5,6] This includes a change of (steroid hormone) metabolism accompanied by the surge of gonadal sex steroids; a change of focus toward (long-term) metabolic complications; psychological issues and treatment adherence; sexual function with a range of gender-specific issues including uro-gynaecological aspects and surgery; fertility aspects including androgen-excess mediated menstrual irregularities in female adolescents and risk of hypogonadism and testicular adrenal rest tumours (TARTs) in male adolescents. Finally, the young person needs to develop independence and autonomy while receiving optimal care when moving from the paediatric to the adult clinic. This transition process needs to be gradually introduced and planned, individualised and include various healthcare professionals experienced in addressing the young person's needs. The transition from paediatric to adult services has been identified as a key element of the holistic care of a person with CAH to reduce long-term morbidity and even mortality.[7] Herein, we review key elements of these challenges and evidence-based management approaches.

2 | CLASSIC CAH AND PUBERTY

The general aim of treating is to replace GC in a dose sufficient to avoid cortisol deficiency and suppress excess adrenal androgen production by reducing ACTH drive while avoiding GC-related adverse effects.[1] Replicating the physiological secretion of cortisol is a challenge and patients often require supraphysiological doses of GCs to achieve therapeutic targets.[1,8]

Clinical observations reveal greater difficulty in achieving adequate control in CAH in the pubertal years despite being on presumed optimal therapy and previous satisfactory control.[5] Poor adherence to medications due to the psychosocial factors of puberty, particularly in an attempt to be more independent and 'normal' is a common encounter. Changing lifestyle with altering sleep-wake patterns and GC dosing frequency also contribute to the increased prevalence of noncompliance in adolescence.[9,10] The influence of alterations in the endocrine milieu on GC pharmacokinetics and changing insulin sensitivity are other possible determinants of suboptimal disease control in puberty.[4,9–11]

2.1 | The endocrine milieu at puberty

Puberty results in several physiological alterations in hormone secretion with the achievement of AH and reproductive capacity (Figure 1). Activation of the hypothalamic–pituitary–gonadal (HPG) axis, which leads to sex hormone production in response to gonadotropins, is the hallmark hormonal signature of puberty. Concurrent growth hormone (GH) secretion and high insulin-like growth factor 1 (IGF-1) lead to the pubertal growth spurt and

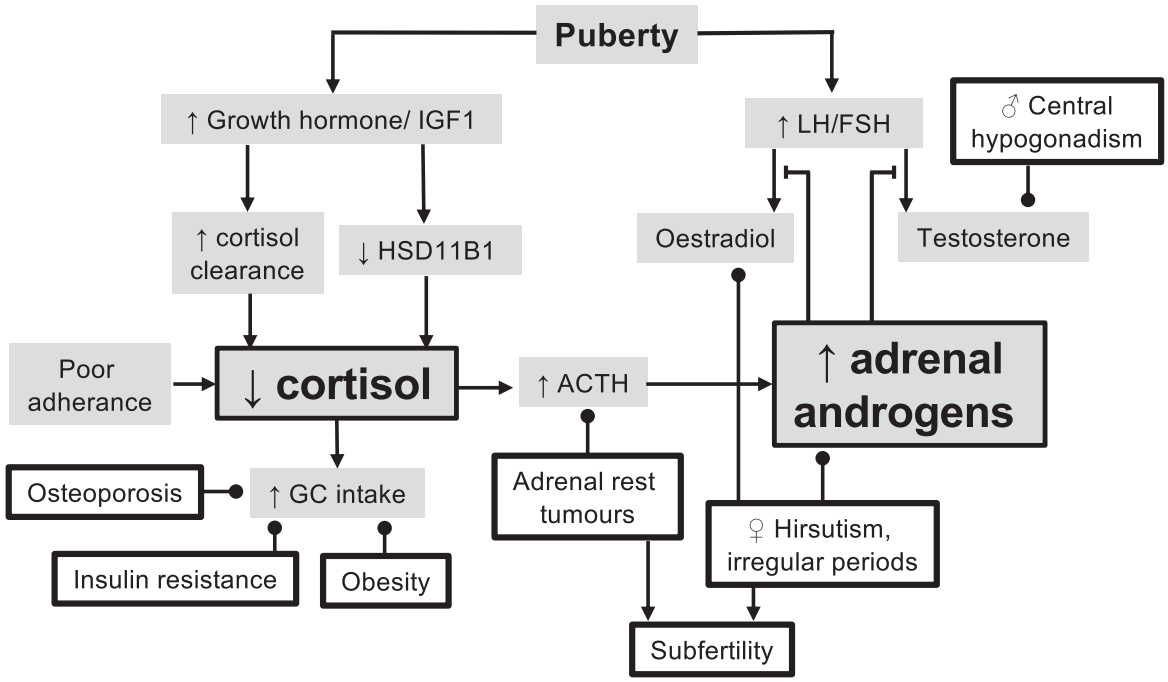

FIGURE 1 Overview of the key hormonal changes that occur at puberty in patients with congenital adrenal hyperplasia, the effects on cortisol metabolism and androgen levels and associated clinical consequences. Glucocorticoid (GC) levels decrease at puberty due to increased renal cortisol clearance, decreased 11β-hydroxysteroid dehydrogenase type 1 activity, mediated by growth hormone and insulin-like growth factor and adherence issues. Lower GC levels results in corticotrophin (ACTH)-mediated increase of adrenal androgen production. Negative-feedback mediated interference of excess adrenal androgens with the hypothalamic–pituitary–gonadal axis may cause central hypogonadism in boys and irregular periods in girls associated with subfertility; ACTH itself increases the risk of adrenal rest tumours; androgen excess itself causes hirsutism in girls. Intensification of GC treatment aims to counteract androgen excess, but increases the risk of associated complications such as osteoporosis, obesity and insulin resistance.

accretion of bone mineral mass.[12] Further, peripheral insulin sensitivity is reduced at puberty with an associated increase in circulating insulin levels.[13]

Cortisol is metabolised primarily in the liver through a cascade of microsomal and cytosolic enzymes, while the kidneys are only contributing to <1% of cortisol secretion.[14–16] Increasing levels of GH and IGF1 at puberty inhibit the catalytic activity of 11β-hydroxysteroid dehydrogenase type 1, which converts inactive cortisone to active cortisol.[17–21] Female adolescents have a higher excretion of cortisol metabolites, pointing toward sex differences in cortisol clearance,[20] possibly explaining why therapeutic control in adolescent girls with CAH is often more difficult to achieve.[10] Higher levels of GH and IGF1 at puberty increase glomerular filtration rate by its direct effect on renal vasculature and by reducing glomerular afferent and efferent arteriolar resistance.[22,23] These alterations lead to an increase in the metabolic/renal clearance of cortisol without changing its half-life in children with classic CAH.[15] The resulting hypocortisolaemia due to reduced GC therapeutic efficiency may further enhance pituitary ACTH drive, leading to a vicious cycle of excess androgen production and increased cortisol clearance (Figure 1).[10,15,24] Androgen excess is further exacerbated by the stimulatory effect of GH, IGF-1 and insulin on enhancing the catalytic activities of CYP17A1 17,20-lyase and HSD3B2.[25–27] Additionally, hyperinsulinism is exacerbated in CAH due to chronic adrenomedullary hypofunction and increased leptin sensitivity, which imposes a direct effect on the adrenals and ovarian theca cells to increase androgen synthesis.[28] Finally, insulin suppresses sex hormone binding globulin and IGFBP-1, increasing free androgens and tissue exposure to IGF1.[29]

These changes pose significant management challenges to combat hypocortisolaemia and subsequent hyperandrogenism, which may result in the observed increased occurrences of adrenal crisis events,[30] menstrual irregularities in females and TART in males (see below; Figure 1) highlighting the need for careful GC dose titration.

To reduce the occurrence of adverse outcomes, treatment intensification should be individualised with careful surveillance of the growth suppressant and adverse metabolic effects associated with higher GC doses.

2.2 | Growth, metabolic outcomes and adrenal crisis

Children with CAH have a lower AH, approximately 1.38 SDs less than the population reference which is also substandard for their familial targets.[31] Puberty is a key determinant of attaining final adult height and has the highest growth velocity beyond infancy.[32,33]

Multicentre studies have demonstrated an attenuated pubertal growth spurt in children with CAH.[32,34]

Children and adolescents with CAH are prone to develop unfavourable metabolic outcomes in later life including hypertension, cardiovascular disease, impaired exercise performance, insulin resistance with impaired glucose tolerance, visceral adiposity, reduced bone mineral density and polycystic ovarian syndrome.[4,35–38] Hyperandrogenaemia per se is known to contribute to increased cardiovascular risk, including increased free fatty acid synthesis, reduced intrahepatic and peripheral insulin sensitivity, low-grade inflammation with oxidative stress and reduced ventricular vascular coupling.[35,39] Therefore, the physiological changes of the endocrine milieu during puberty in adolescents with CAH pose a significant risk for metabolic disturbances in later life.

To avoid adrenal crisis is a key priority in patients with CAH, and to discuss the management of sick-day episodes should happen at every encounter with the children and young people (CYP) and their families in the clinic (Table 1).[1,2,30] In a longitudinal analysis of 156 patients at a single centre over an average of 9 years, the incidence of adrenal crisis events in childhood and adolescence was 10.2/100 patient-years, lower than in adults with 7.2/100 patient-years, but sick day episodes were more often in children.[30] Real-world data

TABLE 1 Overview of the key elements of clinical management in children and adolescents with CAH, emphasising the changes of management aims, implications on clinical surveillance and steroid replacement.

	Childhood	Adolescence
Overall aims	Adequate GC and MC substitution, prevent adrenal crisis	
	Focus on longitudinal growth/height and weight outcomes	Focus on metabolic health, fertility, psychosocial well-being
Management		
Clinic review	*Classic CAH:* – Frequency: 3–4 monthly minimum, during infancy usually more frequent reviews required due to physiological rapid growth and to manage salt wasting – Height, weight, BMI, height velocity, blood pressure – Annual bone age (left hand) (until completion of growth) from 2 years onward – Assessment: GC and MC excess/deficiency, central precocious puberty (breast budding/testicular enlargement) – 17OHP, androstenedione, testosterone, Na/Ka, PRA *Nonclassic CAH:* – Frequency 6–12 monthly – Assess for symptoms of androgen excess – Assess for (partial) adrenal insufficiency (stimulation testing)	*Classic CAH:* – Frequency: 3–4 monthly, 6 monthly after completion of growth – Height, weight, BMI, height velocity, blood pressure – Assessment for GC excess/deficiency – Boys: testicular volumes with palpation for tumours; annual testicular ultrasound from the beginning of puberty – Girls: signs of hirsutism, irregular periods – 17OHP, androstenedione, testosterone, Na/K, renin; Boys: LH/FSH; A:T ratio; annual testicular ultrasound (TARTs) *Nonclassic CAH:* – Frequency 6–12 monthly – Assess for symptoms of androgen excess – Assess for (partial) adrenal insufficiency by stimulation testing
Steroid replacement	*Classic CAH:* – Hydrocortisone 10–12 mg/m^2/day in three to four divided doses o *Consider increase to a maximum dose of 15 mg/m^2/day if high height velocity/BA advancement/androgen excess but ensure compliance first* o *Consider tolerating slightly lower doses in well-controlled patients* o *Consider adjusting dose to normal weight if BMI is high to avoid overtreating* – Fludrocortisone 50–200 mcg/day usually given as once daily dose (SW form); individual adjustment pending on blood pressure, clinical symptoms, electrolyte levels and PRA	*Classic CAH:* – Hydrocortisone 10–12 (–15) mg/m^2/day in three to four divided doses o *Consider increase: TARTs, suppressed LH/FSH with high A:T ratio (>1) (males); hirsutism, irregular periods (girls)* – Fludrocortisone 50–200 mcg/day in one to two doses (SW form); individual adjustment pending on blood pressure, clinical symptoms, electrolyte levels and PRA
	Nonclassic CAH: – Consider Hydrocortisone (low dose) if high height velocity/BA advancement/androgen excess present – Re-evaluate the need for steroid replacement after completion of puberty	*Nonclassic CAH:* – Hydrocortisone (low dose) if androgen excess in girls; wean off in boys in established puberty (Tanner 3, Tvol 10 mL)

Abbreviations: 17OHP, 17-hydroxyprogesterone; BA, bone age; BMI, body mass index; CAH, congenital adrenal hyperplasia; FSH, follicle stimulating hormone; GC, glucocorticoids; LH, luteinizing hormone; MC, mineralocorticoid; PRA, plasma renin activity; SW, salt-wasting; TARTs, testicular adrenal rest tumours.

from an international multicentre study in 518 children (2300 patient-years) reported an incidence of adrenal crisis events as 2.7–3.9 per 100 patient-years with no fatalities and with a higher rate of sick-day events in lower-income countries.[40] A higher rate of hospitalisation was associated with the salt-wasting phenotype, and sick-day episodes were more frequent in late adolescents and toddlers on higher GC doses.[40] Treatment inadequacy due to poor adherence in the adolescent period is a possible explanation for higher incidence of adverse events, prompting the need to emphasise sick day rule training with the provision of adequate resources and equipment, such as emergency passports or bracelets.[30]

2.3 | Treatment

Maintaining optimal control in young adults is paramount to mitigate metabolic risks while avoiding adrenal insufficiency. However, achieving therapeutic goals is a challenge. Supraphysiological GC dose at the onset of puberty imposes a greater risk by increasing hypothalamic somatostatin tone, leading to reduced GH pulses and its direct effect on the growth plate.[4,41] In contrast, too tight control blunts the effect of sex hormones on growth, resulting in reduced height gain.[34,42] There is a lack of consensus on optimal GC dose in puberty, and it is recommended to supplement with the lowest effective dose.[2,42] Generally, it is suggested that boys require a smaller GC dose in puberty as testicular androgen production is more pronounced than adrenal synthesis.[34] A GC dose above 17 mg/m^2/day is associated with significant growth attenuating effects in both sexes and is even more pronounced with prednisolone.[34,43] These findings illustrate the need for meticulous GC dose titration during puberty with regular clinical surveillance.

Serum 17OHP and androstenedione are generally used as biomarkers of GC adequacy, while plasma renin activity (PRA) is used to optimise MC supplementation[1,2] (Table 1). Crucially, laboratory parameters should guide the treatment rather than define the therapeutic target, and other parameters such as growth rate, weight/body mass index (BMI) velocity, blood pressure and bone age assessment should be obtained at every clinic visit to adjust hormone supplementation (Table 1). Current consensus is to monitor 3–4 monthly until growth is completed and optimum control is achieved (Table 1). Steroid biomarkers should be performed consistently considering the timing of hormone replacement and the diurnal variation of hormone secretion. The general goal is to maintain 17OHP close to twice the normal range with near normalisation of androstenedione with PRA in the mid-normal range (Table 1). However, treatment should be individualised, taking the pubertal progression in males and females into account (see below in male- and female-specific sections; Table 1).

Sequential measurements of 17OHP and cortisol over the day, either from (dried) blood, saliva or urine, can be obtained to optimise GC substitution, but is labour-intensive; its availability is often limited due to local resources and commitment of the CYP and their family.[44] Adrenally-derived 11-oxygenated androgens have shown similar but more modest circadian variability as 17OHP or androstenedione and are promising novel biomarkers for therapy monitoring.[9,45] However, their measurements have not been implemented in routine clinical care, and normative reference ranges are yet to be established.[44]

3 | NCCAH AND PUBERTY

NCCAH is considered to be common among inherited diseases with an estimated incidence of 1:1000–1:2000 life births in most Caucasian populations, but even 10 times higher in certain ethnic minorities such as Ashkenazy Jews.[46,47] Since CAH newborn screening does not always detect NCCAH and most patients, especially males, remain asymptomatic even beyond childhood, the condition is often not diagnosed. Androgen excess is the leading symptom if the condition manifests.[48] Based on a systematic review of adolescent and adult cohorts of women with androgen excess, the reported world-wide prevalence of NCCAH is 4.2%, with considerable variation pending on geographical region, ethnic background and sample collection.[49]

The age of puberty onset in NCCAH is generally earlier compared to the general population, however, it is within the accepted age range.[50,51] Central precocious puberty as a presenting feature of NCCAH is reported in some children,[52,53] likely due to a priming effect of chronically elevated androgens on the gonadotrophin releasing hormone (GnRH) pulse generator.[54]

Clinically, symptoms of NCCAH overlap with common androgen excess conditions: Before puberty, children develop early pubic and axillary hair, body odour, sometimes with growth acceleration and advanced bone age, mimicking (idiopathic) premature adrenarche (PA).[55,56] During female adolescence and adulthood, presenting symptoms include menstrual irregularities, hirsutism, acne, alopecia and fertility issues, similar to the symptoms seen in polycystic ovary syndrome (PCOS).[48,55] AH can be attenuated in NCCAH, in particular in CYP with a late diagnosis and significantly advanced bone age at presentation.[57,58]

Since it is not possible to differentiate NCCAH from PA/PCOS on clinical grounds, biochemical testing (and subsequent genetic confirmation) is paramount in all patients presenting with clinical symptoms of androgen excess. An early-morning 17OHP, ideally taken during the follicular phase of the cycle, is the recommended screening test for NCCAH and, if elevated >6 nmol/L (200 ng/dl), should prompt measurement of ACTH-stimulated 17OHP with concomitant measurement of cortisol to assess for GC deficiency. If baseline or stimulated 17OHP exceed 30 nmol/L (1000 ng/dl) (but <300 nmol/L [< 10,000 ng/dL]), NCCAH is biochemically confirmed and should be substantiated with genetic testing.[2,59,60] The diagnosis might be missed in some patients having low early-morning levels of 17OHP, specifically adults.[61,62] In borderline cases, that is mildly raised early-morning 17OHP (>2.5 nmol/L), or if high clinical suspicion (i.e., unusually early-onset of or severe hyperandrogenaemia), second-line testing is warranted.[59] Urinary steroid profiling with gas chromatography/mass spectrometry is likely more sensitive to

detect NCCAH biochemically, but robust data are missing and the method is not readily available in most health-care settings.[63]

3.1 | Cortisol production

Suboptimal stimulated cortisol response has been described in up to 30%–50% of NCCAH patients,[64–67] yet acute adrenal crisis is not often reported.[30] but has led to mortality in a few patients,[68] possibly related to iatrogenic suppression of the HPA axis due to GC treatment.

Hence, the assessment of GC reserve with stimulation testing must be performed in all patients with NCCAH and hydrocortisone stress dose is recommended if there is a suboptimal cortisol response (400–500 nmol/L; 14–18 mcg/L).[2] There is no guidance on re-assessing the HPA axis in patients with a previously normal GC reserve. With the changing hormonal milieu at puberty resulting in increased cortisol clearance and higher GC demands it is possible, that untreated adolescents with NCCAH develop cortisol deficiency. Therefore, a re-evaluation of the HPA axis should be considered during early established puberty, in particular when hyperandrogenic symptoms develop (i.e., rapid bone age acceleration, hirsutism acne) and/or 17OHP levels rise (Table 1).

Mineralocorticoid deficiency is rare in NCCAH. Only one study assessed the renin–angiotensin–aldosterone system response in 20 women with NCCAH with a sodium depletion test and reported higher plasma renin concentrations, but normal blood pressure, aldosterone and electrolyte levels, suggestive of impaired but compensated aldosterone secretion.[67] Therefore, MC substitution is rarely used, only in some cases due to its GC-sparing effect.[59]

3.2 | Treatment

Regular treatment with GC is not generally indicated even though there is a lack of consensus for the optimal approach to treatment and sparse evidence for current recommendations.[2,59] Treatment should be reserved for patients who develop symptoms, which are usually most patients since they have prompted the physician's attention. An individually tailored plan is desired depending on presenting age, severity of presenting symptoms, expecting therapeutic targets considering adverse effects of supraphysiological GC treatment on cardiovascular health and growth.[2,59,69] In addition, maintenance treatment with supra-physiological GC doses increases the risk of iatrogenic adrenal crisis.[30,68] However, children with NCCAH can present with significantly accelerated bone age necessitating GC therapy to suppress the adrenal androgen secretion to improve AH outcomes.[2]

As in classic CAH, hydrocortisone is the GC preparation of choice in children due to its less detrimental effects on growth compared to prednisolone or dexamethasone, but prescribing practices vary considerably.[1] Prednisolone is often preferred as a treatment option in young adults as it requires less frequent dosing and may improve adherence. Considering the adverse metabolic outcomes associated with dexamethasone therapy and its ability to cross the placenta, most clinicians prefer to prescribe prednisolone to young adults.[59] In contrast to classic CAH, lower doses sufficient to suppress adrenal androgen excess are required and should be individualised and titrated.[2,59]

Frequent dose adjustments according to clinical and biochemical markers are necessary to achieve therapeutic targets while avoiding steroid-induced adverse effects and suppression of the HPA axis. In childhood and adolescence, height velocity, bone age and weight/BMI are used to guide GC replacement.[59] The Endocrine Society CAH guideline recommends regular measurements of androstenedione and early-morning 17OHP, although the guidance does not specify treatment targets.[2] 17OHP has a greater variability than androstenedione and is not necessarily a helpful marker in assessing treatment adequacy, despite its usefulness in the diagnostic work-up. In keeping with more recent guidance, it is recommended to keep the androstenedione levels within the age- and sex-specific reference range.[59] 11-oxygenated androgens are probably better markers for treatment monitoring in CAH but are not yet available in routine clinical practice.[45,70]

Upon the completion of puberty and growth, treatment goals in NCCAH change. In asymptomatic women who have achieved AH, discontinuation of GC treatment should be offered.[2] In the adolescent girl with regular menstrual cycles, an individualised approach is required depending on hyperandrogenic features. Female hyperandrogenism and irregular periods can be treated with the combined oral contraceptive pill or with antiandrogenic medications sparing GCs.[5] However, subfertility or recurrent miscarriages might require the reintroduction of GCs at later stages, or if alternative medications to combat hyperandrogenism and irregular periods are not tolerated.

In the adolescent boy in established puberty (Tanner stage 3), the suppression of adrenal androgens with GCs is questionable and GC should be discontinued before the pubertal growth spurt occurs (Testicular volume 8–10 mL).[5] Steroid tampering must be done with caution. All patients should be assessed for adrenal insufficiency and may require stress dosing.

In conclusion, maintenance therapy with GCs is not routinely indicated in children and adolescents with NCCAH, and should be guided by the presence of hyperandrogenic symptoms. Patients need an individualised treatment plan depending on symptoms with careful assessment of growth parameters and surveillance for cardiovascular risk.

4 | MALE-SPECIFIC ISSUES

Gonadal dysfunction is a common complication in males with classic CAH, which may arise during adolescence leading to subfertility in later life.[6,71] The key risk factor causing gonadal dysfunction is poor hormonal control with excess adrenal androgen production causing gonadotrophin suppression with secondary hypogonadism (Figure 1).

Excess ACTH is thought to be one of the key drivers for the development of TARTs, which, if untreated, can cause primary hypogonadism (Figure 1). Close surveillance of gonadal function with optimisation of hormonal control is, therefore, a key aim in managing boys with classic CAH during adolescence and beyond.

4.1 | Secondary hypogonadism

At puberty, excess adrenal androgens in poorly controlled CAH are aromatised to oestrogens and suppress gonadotrophin secretion from the anterior pituitary, leading to hypogonadotropic hypogonadism.[71–73] Abnormal gonadal function attributed to HPG axis disturbances was reported in various cohorts of CAH men at different ages, ranging from 20% to 52%.[74–80] In a large French sample of 219 men with predominantly classic CAH (median age 32 years) gonadotrophin levels were low/suppressed in more than one-third of men.[78] The dsd-Life study assessed gonadal function in 121 adult CAH men (median age 28 years), and nearly half of them had abnormalities in the HPG axis[79]; more detailed hormonal assessment in a subsample showed that reduced gonadotropin concentrations were associated with lower testosterone and, more strongly, with a high androstenedione to testosterone (A:T) ratio (≥1), indicating that excess adrenal androgens suppress the HPG axis.[79] Indeed, the androgen precursor androstenedione is frequently elevated in poorly controlled CAH,[81] and is further converted outside the adrenal to testosterone and dihydro-testosterone.[82] Currently, there is no method that would distinguish testosterone derived from the adrenals or from testicular Leydig cells. Therefore, the A:T ratio with simultaneous measurement of gonadotrophins has been suggested to be a useful *proxy* marker to assess adrenal control in classic CAH at puberty and beyond.[81] Since little androstenedione from the testes is found in the circulation from puberty onward, a ratio of <0.2 suggests good control; a ratio of 0.5 or higher is indicative of excess adrenal androgen production and a ratio of 1.0 or higher (with suppressed LH/FSH) suggests excess testosterone generation originating from the adrenal.[1,71,79,81] The suggested cut-offs are mainly based on expert opinion[71,81] with limited validation in larger cohorts, mainly in young adult men,[79,80] and long-term studies with a comprehensive assessment of the HPG axis from puberty onward are needed.

11-oxygenated androgens have been shown to be marker metabolites for disease control in CAH.[45,83] While these findings are still to be translated into the routine clinical management of CAH, the question arises if 11KT also influence the HPG axis, exacerbating secondary hypogonadism in poorly controlled CAH. In a German cohort with 39 adult classic CAH men (median age 28 years), 23% showed a biochemical picture of hypogonadotropic hypogonadism, but in those 11KT or 11hydroxy-androstenedione were not disproportionally elevated compared to the classic androgens androstenedione or 17OHP.[80] The A:T ratio, however, correlated stronger with low gonadotrophin levels.[80] Mechanistically, oestradiol derived from aromatisation of testosterone, modulates the GnRH pulse generator and gonadotrophin release in the anterior pituitary.[73] Recent in vitro/ex vivo studies have shown that 11-oxygenated androgens can be aromatised and activate the oestrogen receptor.[84] However, in vivo, 11-oxygenated oestrogens are not detectable in plasma of pregnant women (with high placental aromatase activity), nor in patients with CAH,[84] questioning the contribution of adrenal-derived 11-oxygenated androgen excess of HPG axis dysfunction in CAH.

In summary, the A:T ratio with simultaneous gonadotrophin measurement and assessment of the testicular size are useful tools to detect HPG axis disturbances in the CAH adolescent and should be performed at every clinic visit.[71]

4.2 | TARTs and primary hypogonadism

TARTs are a common complication in boys and men with classic CAH.[72] Their origin is thought to be aberrant adrenal cells, situated in the centre of the testis, and stemming from a common adrenal/gonadal progenitor.[72] Due to their adrenal cellular characteristics,[85] they respond to ACTH explaining why the size/severity of TARTs is associated with poorer disease control. Mass effects caused by the tumour may lead to testicular damage causing primary hypogonadism with impaired fecundity and infertility.

In the paediatric/adolescent age group, the reported prevalence of TARTs in selected, mostly retrospective cohorts range from 10% to 40%.[86–96] It is unusual that TARTs are detected before puberty (median age: 13 years).[97] However, the youngest reported patient is 18 months old.[94]

TARTs can be identified by palpation, but their deep central location in the *rete* testes only allows larger lesions above 2 cm to be identified in that way.[72] Imaging techniques diagnose lesions of several millimetres in size, and ultrasound is the preferred mode of investigation due to the accessibility of the testes. TARTs usually present as hypoechogenic lesions on ultrasound.[98] It can be challenging to discriminate TARTs from other tumours, especially Leydig Cell Tumours, since they appear similar on imaging, are commonly situated centrally in the testis and have similar cellular and molecular characteristics.[72] Since Leydig-cell tumours, in contrast to TARTs, are more likely to progress to cancer in adulthood,[99,100] surgery is the treatment of choice, in contrast to TARTs, which are currently only removed if they become symptomatic due to pain or mass-related discomfort.[101,102] Helpful aids to differentiate between TARTs and Leydig-cell tumours are the unilateral presence of Leydig cell tumours (90% vs. about 20% in TARTs), and that they rarely occur in men with CAH.[103] whereas TARTs are common.

There is limited published guidance on the treatment and prevention of TARTs. Regular screening should begin in adolescence[2] or even from 8 years onward[72] annually with testicular ultrasound; since the risk of TARTs is higher in patients with poor disease control or late diagnosis, patient-specific circumstances should be considered. Case reports indicate that intensified GC treatment may lead to a reduction in tumour size with improved testicular function.[104–106] However, GC-induced side effects with stunted adolescent growth

are limiting this approach.[43,107] Other pharmacological interventions, such as mitotane or gonadotrophin replacement therapy are reported in single and extreme cases.[108,109] Testis-sparing surgery has been explored in small case series of boys and men with 'steroid-unresponsive' TARTs, which has led to no improvement of testicular function,[102,110,111] suggesting that surgery should only be indicated in cases where tumour-associated discomfort or even pain occur.[6,72,79] Since infertility is a key risk factor in patients with TARTs, appropriate counselling at a young age should be done, also to improve treatment adherence, which reduces the risk of further tumour growth. When ready, the adolescent or young adult should be referred for consideration of semen analysis and storage.

5 | FEMALE-SPECIFIC ISSUES

Female adolescents with CAH are at risk of abnormal pubertal development and often develop menstrual disturbances with clinical signs of androgen excess, such as hirsutism and acne, similar to the clinical picture of PCOS, resulting in subfertility in later life.[6] However, despite the risk for CAH girls to develop central precocious puberty, the overall timing of adrenarche and puberty, including the age of menarche, does not seem to differ in girls with CAH compared to controls,[112–114] taking into account the high degree of menstrual irregularities in the general population.[113] Poor therapeutic control with excess production of adrenal androgens is a key factor exacerbating gonadal dysfunction by directly interfering with the hypothalamic–pituitary–ovarian axis. Similar to males with CAH, excess adrenal androgens interfere with the GnRH pulse generator and cause menstrual disturbances with anovulatory cycles and lead to the development of polycystic ovaries.[2,6] In addition, accumulating steroid precursors, such as 17OHP and progesterone, may have a direct effect on the endometrial linen which fails to thicken adequately causing primary amenorrhoea.[115] An assessment of menstrual regularity of the female adolescent/young adult with CAH should, therefore, be done at every clinic visit and may be an indicator of good therapeutic control.[2] Ensuring good compliance and possible intensification of GC therapy with balancing the implications of overtreatment are the most appropriate management considerations in the adolescent with irregular periods. Measurement of 17OHP, androstenedione, testosterone, progesterone and gonadotrophins with oestradiol is essential to establish a hormonal cause for irregular periods and poor therapeutic control.[6,116]

Ovarian adrenal rest tumours (OARTs) are a rare entity in CAH females, far less frequent than TARTs and mostly reported as individual cases in patients with a late diagnosis or extremely poor disease control.[117–127] Several reported patients have had bilateral adrenalectomy inevitably resulting in chronically elevated ACTH levels, increasing the risk of ART development.[120,121,123,124,127,128] The difficult access of the intra-abdominally located ovaries to ultrasound imaging may explain the low reported prevalence of OARTs. However, MRI imaging in a small cohort of young classic CAH females (age 15–24 years) did not detect OARTs in 13 individuals studied.[129] Functional imaging with radio-labelled tracers in combination with pelvic venous sampling might be more powerful in detecting smaller lesions and has been employed in selected cases.[128,130] Routine imaging surveillance for OARTs is, therefore, not recommended in females with CAH.[2,6] OARTs screening should be considered in patients who experience an excessive surge of androgens excess despite being on adequate supra-physiological GC doses or postbilateral adrenalectomy.

5.1 | Surgical complications

Genital surgery in 46,XX CAH patients has been employed for several decades and its timing and methodology is a matter of current ongoing debate. The Endocrine Society guideline recommends an individualised, patient/family-centred approach and advises on delaying surgery until the child is older and has reached full capacity to be involved in decision-making.[2] In severely virilised females, early surgery to repair the urogenital sinus might be considered and decisions must remain in the prerogative of the families. Nevertheless, a high number of CAH girls at adolescent age have undergone surgical procedures, and typically at puberty and beyond adolescence complications may arise, which can be anatomical and psychological. There is a paucity of good-quality prospective data on long-term outcomes on sexual function and quality of life in CAH girls who have had early reconstructive surgery. However, recently the dsd-Life study group has reported outcomes in 176 adult CAH women with classic CAH, including surgical outcomes and patient-reported outcomes.[131] A high degree of atypical anatomy was reported upon gynaecological examination in about half of the sample, including absent (9.5%) or abnormal (36.7%) clitoris, abnormal-looking large labia (22.6%), absent small labia (23.8%), no vaginal introitus/single opening (5.1%), scarring (86.2%) and vaginal stenosis (16.5%); 61.5% of women were satisfied with the cosmetic outcome, 61.9% with functionality and 37.4% with sex life.[131]

The adolescent girl with CAH who has had surgery, therefore, may present with various issues, which commonly include urinary incontinence, recurrent urinary tract infections, clitoral discomfort, vaginal stenosis and cosmetic concerns.[5] To address most of these issues effectively and sensibly, the young person needs a comprehensive assessment by an expert paediatric urologist and/or urogynaecologists, preferably the person who has performed the surgery in the first place. Support from a clinical psychologist experienced in the management of patients with CAH should be sought to ensure holistic management.

6 | TRANSITION TO ADULT CARE

The transition of care from paediatric to adult services is defined as a 'multi-faceted, active process that attends to the medical, psychosocial and educational/vocational needs of adolescents as they move from child-centred to adult-orientated care'.[132] Transition is a

gradual, ongoing process starting early in the paediatric clinic and continues after transfer has occurred to adult services.[133,134]

Poor transition processes have been identified in patients with complex chronic diseases, including CAH, and potentially worsen long-term medical and psychosocial health outcomes. In the UK-CaHSE study, conducted from 2004 to 2007, only a minority of adult patients are under specialist endocrine care.[77] The transition process of CAH patients to adult care is challenging even in tertiary endocrine centres where there is close collaboration between paediatric and adult endocrine teams.[135]

At the same time as the transition of healthcare, adolescents are navigating the biological changes of puberty, including growth and sexual maturation; psychologically, they are beginning to develop their own identity, morality and abstract thinking; socially, they may be experiencing changes in their relationships with family and friends in the process of developing autonomy. Some of these aspects of adolescence can be impacted on by having a chronic endocrine condition, in particular CAH. Consequently, there is an increasing focus on delivering developmentally appropriate healthcare, of which effective transition is simply an aspect.

The gradual process of transition should start from the age of 11–13 years and should extend until the age 23–25 to give the young person the flexibility to develop at their own pace.[133,136,137] It is crucial to recognise that the transition does not end with the transfer to adult service and needs to continue after transfer with the consolidation of acquired knowledge and self-skills to increase confidence and autonomy.[134] Holistic transition services, therefore, need to adopt a 'push' approach from paediatrics as well as an effective 'pull' from adults that meets the individual needs of the patient, as advocated in the United Kingdom as an outcome from the Children's and Young People's Health Outcome Forum.[134]

The ultimate aims of the successful transition of young people with CAH are (1) to empower and educate the young person to take on the responsibility of their health condition, which includes an understanding of the disease and its implications; (2) to minimise long-term adverse health outcomes associated with poor transition processes and (3) to ensure appropriate and sustained follow-up with adult healthcare professionals, including adequate transfer of all relevant information.[135,138]

A recent UK study exploring effective transition in chronic conditions identified a range of evidence-based healthcare interventions. The three key interventions were encouraging self-efficacy, meeting the adult team before transfer, and appropriate involvement of parent or carer.

With the shift of focus from the carer to the young person during the transition period moving (Table 1), the consultation is the ideal place to facilitate this by making the young person the centre of the consultation, encouraging self-efficacy, by enabling empowerment

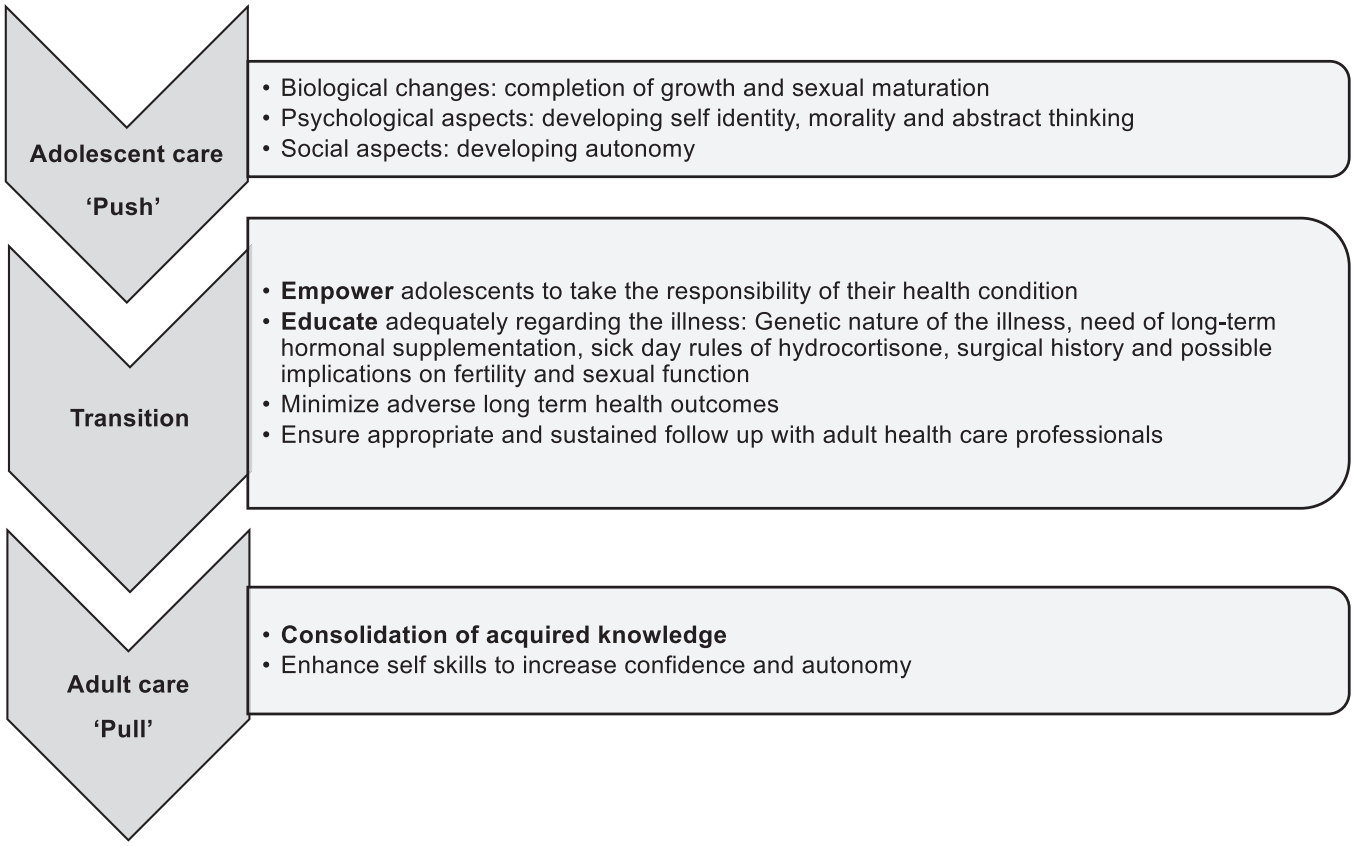

FIGURE 2 Overview of elemental management goals during the transition from adolescent to adult care of patients with congenital adrenal hyperplasia.

and education. Young people with CAH should acquire knowledge to allow them to feel confident to ask questions within defined areas of their condition, and it is helpful to define those goals as part of the transition process and review them regularly during clinic visits. These goals may include[5] (1) the nature of their condition and understanding the genetic background with a possibility that it can be passed on/need for genetic counselling for pregnancy planning; (2) the need for hormone supplementation and the consequences of GC over- and undertreatment; (3) the importance of maintaining their safety, including being able to apply 'sick day rules', including intramuscular injections of hydrocortisone; (4) female patients know about their surgical history and possible implications on sexual function and delivery. The achievement of these goals should occur at the right pace for the young person.[5] Support and counselling for caregivers should be offered to assist with this process.[5] Adolescent girls and adult women with CAH have a higher degree of anxiety disorders and altered body image,[139–141] emphasising the need for a sensitive, tailored approach with experienced psychological support at this time.[142,143]

While encouraging the development of independence is vital for adulthood, support toward achieving this independence must encompass a holistic approach in keeping with the young person's maturity, cognitive abilities and psychological status.[137] This may include the young person's views on to what extent they would like their parents or carers to be involved in aspects of their care. If appropriate, it can be beneficial to encourage young people to attend consultations by themselves to encourage independence.

A staged approach from encouraging independence to ensuring transitional readiness is important as the transfer itself is only a single event within the transition process (Figure 2). This process should embody a strengths-based approach where transition options should be based on what the patient feels is positive and possible.[137] From there on, small steps may be taken to support young people with decision-making so they can gradually gain confidence in self-caring.[137,144]

The transfer to adult services then depends on when the young person feels prepared and demonstrate increasing autonomy, when they feel in control of their condition, and provided consideration has been given to other aspects of their life to ensure sufficient stability.[7] Identifying the right time for transfer ('transition readiness') is subject of ongoing research. Self-reported transition readiness was prospectively assessed in a small sample of CAH adolescents and young adults through modified disease-specific questionnaires and 'good readiness' associated with medication adherence rates.[7] In addition, gaps in knowledge such as uncertainties how to adjust medication during stress/intercurrent febrile illness ('sick day rules') can be identified.[7,145]

Structured transition programmes have been found to be effective in chronic disease, such as type 1 diabetes, and improve adherence, health outcomes and quality of life,[146,147] but no data exist for young people with CAH. The generic 'Ready Steady Go' programme has been successfully implemented in various hospitals in the United Kingdom, including our centre, as part of routine adolescent transitional care.[148]

The introduction of the adult team within the paediatric setting in joint clinics (or 'transition clinics') has been shown to have a positive effect on health outcomes. Some studies have failed to show effectiveness, which emphasises that a joint clinic alone is not enough.[133,135,149] They provide young people and families with the opportunity to meet the adult team, facilitate familiarisation with adult care facilities and reduce the risk of clinical information getting lost at the point of transfer.[133,135]

In summary, the transition of young people with CAH from paediatric to adult care is important in ensuring endocrine care is provided seamlessly across the lifespan. Recognising that transition is part of developmentally appropriate healthcare will ensure that the holistic needs of this age group are met. Research has identified the three key elements are encouraging self-efficacy, appropriate involvement of carer and meeting the adult team before transfer.

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