Congenital adrenal hyperplasia

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Congenital adrenal hyperplasia is a group of autosomal recessive disorders encompassing enzyme deficiencies in the adrenal steroidogenesis pathway that lead to impaired cortisol biosynthesis. Depending on the type and severity of steroid block, patients can have various alterations in glucocorticoid, mineralocorticoid, and sex steroid production that require hormone replacement therapy. Presentations vary from neonatal salt wasting and atypical genitalia, to adult presentation of hirsutism and irregular menses. Screening of neonates with elevated 17-hydroxyprogesterone concentrations for classic (severe) 21-hydroxylase deficiency, the most common type of congenital adrenal hyperplasia, is in place in many countries, however cosyntropin stimulation testing might be needed to confirm the diagnosis or establish non-classic (milder) subtypes. Challenges in the treatment of congenital adrenal hyperplasia include avoidance of glucocorticoid overtreatment and control of sex hormone imbalances. Long-term complications include abnormal growth and development, adverse effects on bone and the cardiovascular system, and infertility. Novel treatments aim to reduce glucocorticoid exposure, improve excess hormone control, and mimic physiological hormone patterns.

Introduction

In 1865, Luigi De Crecchio, an Italian pathologist, described the case of a man who, at autopsy, was found to have female internal anatomy and large adrenal glands, representing the first known case of presumed congenital adrenal hyperplasia (figure 1).[1] However, treatment for congenital adrenal hyperplasia was not introduced for almost another century when cortisone was given for what was then known as adrenogenital syndrome.[18–22]

Congenital adrenal hyperplasia is a group of seven autosomal recessive diseases caused by mutations in genes encoding enzymes in pathways involved in cortisol biosynthesis: 21-hydroxylase (21OH), 11β-hydroxylase (11βOH), 17α-hydroxylase (17OH; also known as 17,20-lyase), 3β-hydroxysteroid dehydrogenase type 2 (3βHSD2), steroidogenic acute regulatory protein (StAR), P450 cholesterol side-chain cleavage enzyme (SCC), and P450 oxidoreductase (POR). Multiple hormonal imbalances occur and congenital adrenal hyperplasia manifests with a range of clinical and biochemical phenotypes, with or without alterations in glucocorticoid, mineralocorticoid, and sex steroid production. Both severe (classic) and mild (non-classic) forms of congenital adrenal hyperplasia have been described.

More than 95% of congenital adrenal hyperplasia cases are due to 21OH deficiency,[23] characterised by impaired cortisol and aldosterone production and androgen excess. Life-saving neonatal screening for classic congenital adrenal hyperplasia due to 21OH deficiency was first done in Alaska in 1977,[7] and is currently used worldwide in more than 40 countries, including all 50 US states since 2009, although it is yet to be implemented in the UK.[7,23–25] Although all types of classic congenital adrenal hyperplasia are rare orphan diseases, the non-classic form due to 21OH deficiency is estimated to be one of the most common autosomal recessive disorders.[26,27]

Congenital adrenal hyperplasia remains one of the most challenging endocrine disorders to diagnose, manage, and treat because of the disorders' direct and indirect effects on steroidogenic pathways and the rarity of these conditions. Advances in genetics, metabolomics, and treatment strategies continue to improve understanding of these complex diseases and aim to improve patient outcomes.

Search strategy

We searched the Cochrane Library, MEDLINE, and Embase between Jan 1, 2010, and Sept 30, 2016. Keywords and controlled vocabulary and their synonyms were used when appropriate. We used variations of the search term "congenital adrenal hyperplasia" in combination with the terms "diagnosis/diagnostics", "genetics", "genomics", "adrenal crisis", "glucocorticoid", "mineralocorticoid", "gene therapy", "quality of life", "well-being", "screening", "metabolomics", "prenatal", "antenatal", "bone mineral density", "tumor", "pregnancy", "treatment/therapy/ therapeutic", "fertility/fecundity", "surgery", "management", "metabolic", and "complications". We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. The search was restricted to English publications.

Genetics and pathophysiology

Overview

All types of congenital adrenal hyperplasia are monogenetic and autosomal recessive. Most patients are compound heterozygotes, meaning that they have different mutations in two alleles for a particular gene. The clinical manifestation follows the allele that results in a more functional enzyme, and generally genotype–phenotype correlation is good.[28,29]

Adrenal steroidogenesis occurs by a series of steps facilitated by adrenal zone-specific enzyme expression, and in different types of congenital adrenal hyperplasia this process is interrupted at distinct points. In addition to the classic well established steroidogenesis pathway, an alternative pathway to active androgen biosynthesis exists (termed the backdoor pathway),[30,31] which might play a role in the pathophysiology of congenital adrenal hyperplasia (figure 2). The clinical manifestation of congenital adrenal hyperplasia is closely related to the type and severity of impairment.

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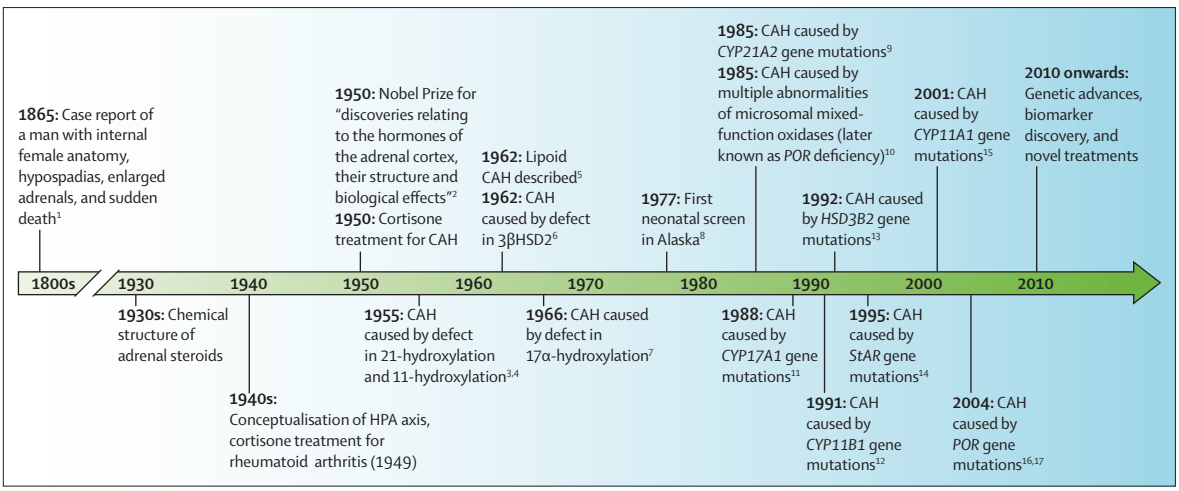

Figure 1: **Timeline of important discoveries in adrenal steroidogenesis, treatment landmarks, and gene discovery of congenital adrenal hyperplasia**
HPA=hypothalamic-pituitary-adrenal. CAH=congenital adrenal hyperplasia. 3βHSD2=3β-hydroxysteroid dehydrogenase type 2 deficiency. POR=P450 oxidoreductase.

21OH deficiency

The gene for 21OH, *CYP21A2*, is located within the human leucocyte antigen class III region of chromosome 6 (table 1). *CYP21A2* and a homologous pseudogene, *CYP21A1P*, lie about 30 kb apart. Meiotic recombination events are common in this genomic region because of the high degree of sequence homology between duplicated genes. Approximately 95% of *CYP21A2* disease causing mutations are *CYP21A1P*-derived variants or deletions due to recombination events.[28,39]

Defective 21OH-hydroxylation results in decreased glucocorticoid and mineralocorticoid synthesis and elevated precursors, most notably 17-hydroxyprogesterone (17OHP), which is used for congenital adrenal hyperplasia diagnosis (figure 2). Adrenocorticotropic hormone (ACTH)-stimulated androgen production occurs because no block exists in the pathway synthesising adrenal androgens.

Conventionally, classic 21OH deficiency is sub-classified into salt wasting and simple virilising forms, which reflect the severity of aldosterone deficiency. Mutations that completely inactivate *CYP21A2* result in the salt-wasting phenotype, which, without neonatal screening, presents in the first 2 weeks of life with a life-threatening adrenal crisis (table 2).[23] Patients with classic simple virilising congenital adrenal hyperplasia have mutations that retain 1–2% of 21OH activity and minimal aldosterone production prevents a neonatal crisis.[40] Excess fetal adrenal androgen exposure results in virilisation of external genitalia of 46,XX patients with classic 21OH deficiency (salt wasting and simple virilising; figure 3A). Without neonatal screening, male toddlers with the simple virilising form of the disorder are diagnosed with signs and symptoms of androgen excess. Postnatal excess androgen presence leads to premature growth of pubic hair and rapid skeletal growth in children. Patients with the non-classic form retain up to 50% of enzyme activity and mostly do not have adrenal insufficiency, but might have partial glucocorticoid deficiency, and female patients have normal genitalia.[41] Patients might present with mild androgen excess or have few or no symptoms. In fact, the term cryptic congenital adrenal hyperplasia was created to define patients with non-classic congenital adrenal hyperplasia who are identified by family genetic studies, but are otherwise asymptomatic.[42]

11βOH deficiency

Congenital adrenal hyperplasia caused by 11βOH deficiency is due to *CYP11B1* mutations (table 1). The enzyme encoded by *CYP11B1* functions in the adrenal zona fasciculata to convert 11-deoxycortisol to cortisol and deoxycorticosterone to corticosterone under the regulation of ACTH (figure 2). Most *CYP11B1* mutations correspond to minimal or absent enzyme activity, resulting in a classic congenital adrenal hyperplasia phenotype.[43]

Impaired 11-hydroxylation results in decreased corticosterone and cortisol synthesis, with subsequent increase in ACTH and excess androgens, caused by shunting of the pathway towards androgen production. Normally corticosterone and deoxycorticosterone production by *CYP11B1* transcription in the adrenal zona fasciculata is minimal, but deoxycorticosterone concentrations can rise substantially under the influence of ACTH.[44] Deoxycorticosterone is a weak mineralocorticoid, but elevated concentrations of deoxycorticosterone suppress the renin–angiotensin system, resulting in extracellular fluid volume expansion, hypertension, low plasma renin activity, and low aldosterone concentrations, although the ability to produce aldosterone remains.[32] The effects of

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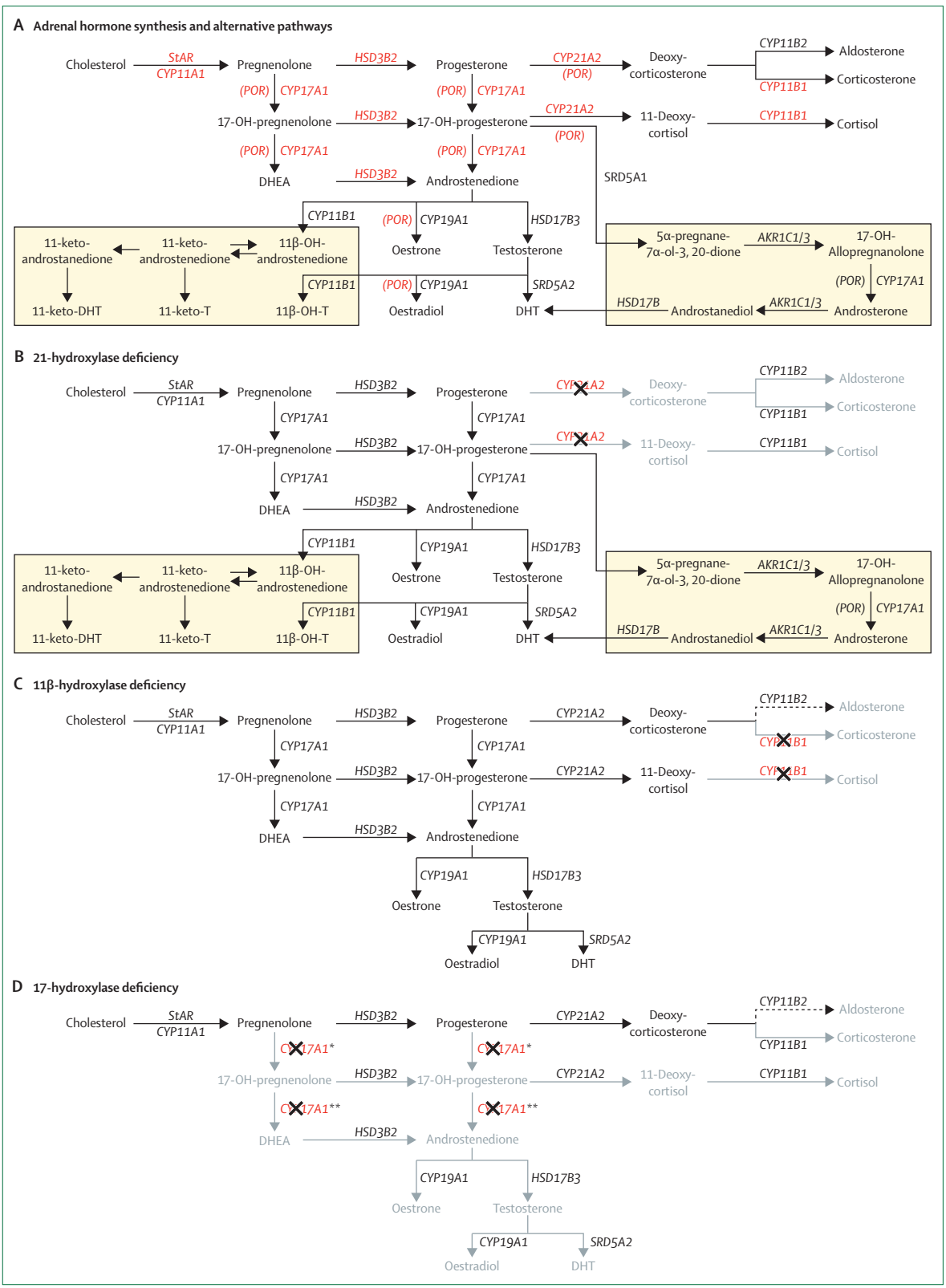

(Figure 2 continues on next page)

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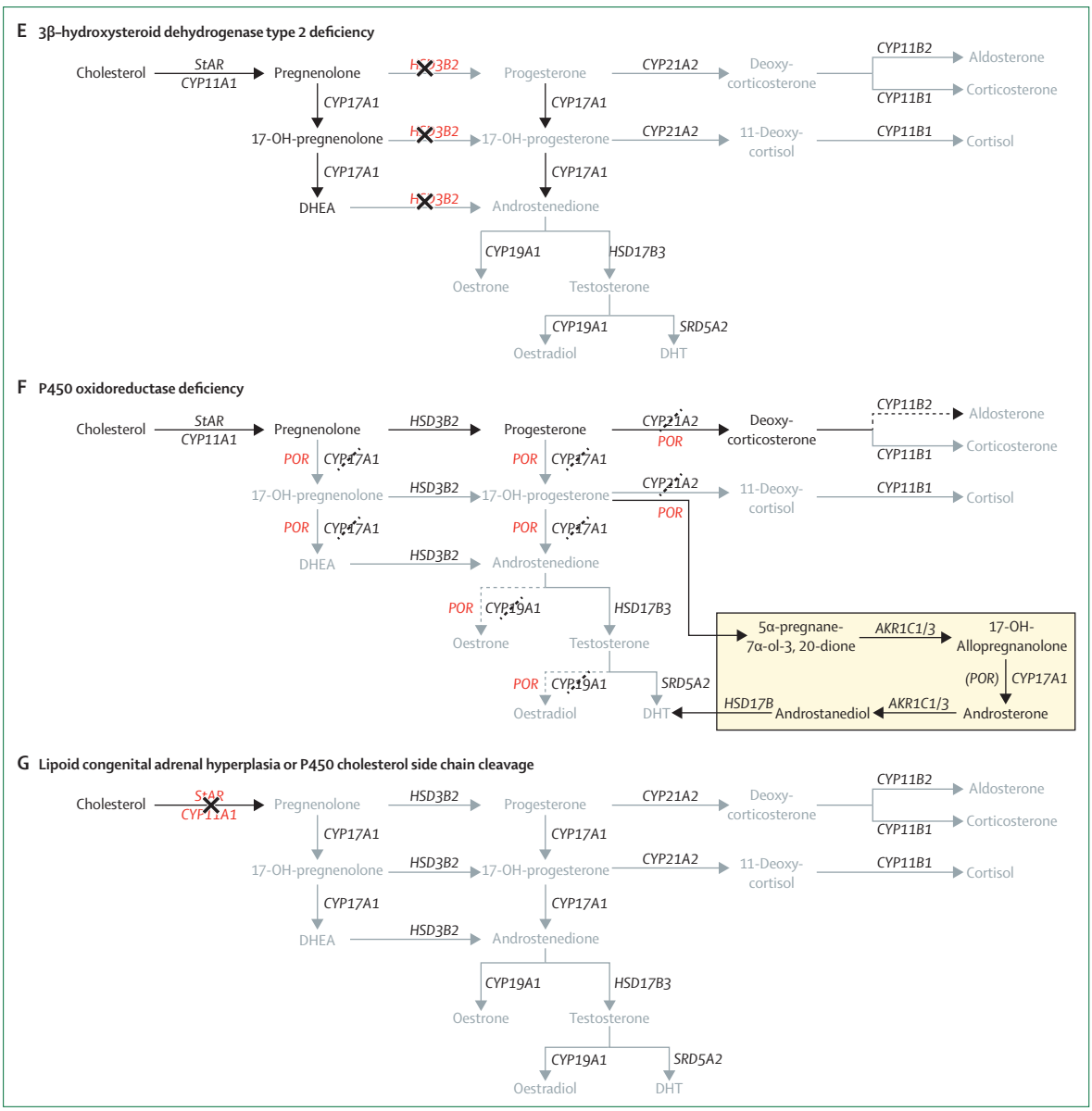

Figure 2: **Adrenal steroidogenesis pathways**
(A) Classic steroidogenesis pathway and alternative pathways leading to androgen production in the light yellow boxes. (B) 21-hydroxylase deficiency, (C) 11β-hydroxylase deficiency, (D) 17-hydroxylase deficiency, (E) 3β-hydroxysteroid dehydrogenase type 2 deficiency, (F) P450 oxidoreductase deficiency, and (G) lipoid congenital adrenal hyperplasia and P450 cholesterol side chain cleavage deficiency, with impact of specific impairments on the adrenal steroidogenic pathway. Genes in which mutations cause congenital adrenal hyperplasia are shown in red. Light grey denotes deficient hormones at low concentrations due to the preceding block in steroid production. Dashed arrows denote indirect suppression of the subsequent hormone. Dashed lines across enzymes denote apparent enzyme deficiency. DHEA=dehydroepiandrosterone. DHT=5α-dihydrotestosterone. T=testosterone. POR=P450 oxidoreductase.

renin–angiotensin system suppression might not occur in the neonatal period because of renal mineralocorticoid resistance that is present in the first few months of life. Clinically, patients with 11βOH deficiency present similarly to patients with 21OH deficiency with signs of androgen excess, but patients with 11βOH also have hypertension rather than salt loss (table 2).[32] A non-classic form of enzyme deficiency caused by *CYP11B1* mutations exists but is very rare.[45]

17OH deficiency

The *CYP17A1* gene encodes an enzyme that expresses both 17α-hydroxylase and 17,20-lyase activities (table 1). Because of the location of the enzyme in the steroidogenic pathway, severe mutations in the gene impair adrenal and gonadal sex steroid production (figure 2), which causes sexual infantilism and puberty failure (table 2).[35] Production of dehydroepiandrosterone is blocked, which prevents adrenarche and development of pubic and axillary hair.

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	21-hydroxylase deficiency	11β-hydroxylase deficiency	17α-hydroxylase/ 17,20-lyase deficiency	3β-hydroxy-steroid dehydrogenase type 2 deficiency	P450 oxidoreductase deficiency	Lipoid adrenal hyperplasia	Cholesterol side chain cleavage enzyme deficiency
Affected gene (OMIM number)	*CYP21A2* (201910)	*CYP11B1* (202010)	*CYP17A1* (202110)	*HSD3B2* (201810)	*POR* (201750)	*StAR* (600617)	*CYP11A1* (118485)
Incidence	Classic: 1:10 000 to 1:20 000[25] Non-classic: 1:200[27] to 1:1000[26]	1:100 000[32] in Caucasians, 1:6000[33] in Moroccan Jews* Non-classic: unknown	1:50 000[34] Increased frequency in Brazil*[34,35]	Rare	Rare, 130 cases from 11 countries reported[36]	Rare, mostly Japanese, Korean, and Palestinian populations [37]	Rare, <30 patients, mostly from eastern Turkey[38]
Affected organs	Adrenal glands	Adrenal glands	Adrenal glands and gonads	Adrenal glands and gonads	Adrenal glands, gonads, liver, and skeletal	Adrenal glands and gonads	Adrenal glands and gonads
Disorder of sex development	Classic: 46,XX Non-classic: No	Classic: 46,XX Non-classic: No	46,XY	Classic: 46,XY, 46,XX (rare) Non-classic: No	46,XX, 46,XY (variable)	46,XY Non-classic: 46,XY (variable)	46,XY Non-classic: 46,XY (variable)
Salt wasting	Classic: Yes Non-classic: No	No	No	Yes	No	Classic: yes Non-classic: minimal to none	Classic: Yes Non-classic: minimal to none
Hypertension	No	Yes Non-classic: variable	Yes	No	Yes	No	No
Postnatal virilisation	Classic: yes Non-classic: yes	Classic: Yes Non-classic: Yes	No	Classic: 46,XX Non-classic: 46,XX	No	No	No
Sex steroid deficiency	No	No	Yes	Classic: Yes Non-classic: No	Yes	Yes Non-classic: variable	Yes Non-classic: variable
Other	..	..	..	..	With or without skeletal malformations With or without maternal virilisation	..	..

OMIM=Online Mendelian Inheritance in Man. POR=P450 oxidoreductase. StAR= steroidogenic acute regulatory protein. *Due to presence of a founder mutation.

Table 1: **Genetic causes and clinical features of the various forms of congenital adrenal hyperplasia**

CYP17A1 is expressed in the adrenal zona fasciculata and zona reticularis but not in the zona glomerulosa. Therefore, ACTH-mediated steroidogenesis results in elevated concentrations of deoxycorticosterone and corticosterone. High concentrations of deoxycorticosterone cause sodium retention, hypertension, and hypokalaemia, with suppression of aldosterone production. The presence of corticosterone, which has glucocorticoid activity, prevents patients from having an adrenal crisis, even though cortisol production is low or absent. Both 46,XX and 46,XY patients with 17OH deficiency have female external genitalia and usually present during puberty as girls without secondary sexual characteristics, with hypergonadotropic hypogonadism, and low-renin hypertension (table 2). Isolated 17,20-lyase-deficiency has been reported[46] but is extremely rare and in truly isolated forms is caused by mutations in cytochrome b5, the co-factor needed by CYP17A1 to exert 17,20 lyase activity.[47] Although phenotype variability occurs, a non-classic form with subtle clinical manifestations has not been defined.

3βHSD2 deficiency

3β-hydroxysteroid dehydrogenase exists in two isoforms, type 1 (3βHSD1) and type 2 (3βHSD2), which are encoded by *HSD3B1* and *HSD3B2* genes, respectively (table 1). The *HSD3B2* gene is highly expressed in the adrenals and gonads, while *HSD3B1* is expressed in the placenta and peripheral tissues.

Impaired 3βHSD2 functionality results in decreased concentrations of aldosterone, cortisol, and androstenedione, with a subsequent increase in the concentrations of renin, ACTH, and dehydroepiandrosterone (figure 2). Dehydroepiandrosterone can be converted to testosterone by extra-adrenal 3βHSD1. Patients present in infancy with a salt-wasting adrenal crisis, underdeveloped 46,XY genitalia, and rarely 46,XX virilisation (table 2).[48]

The hormonal criteria for diagnosis of 3βHSD2 deficiency have changed over the past three decades because the initial studies identifying a possible non-classic form were not based on genetic findings and subsequent genetic studies failed to confirm the diagnosis.[49–51] Non-classic 3βHSD2 deficiency exists, but is extremely rare.

POR deficiency

POR plays a key role in electron transport in the endoplasmic reticulum, and several enzymes including 17OH, 21OH, and aromatase depend on POR for their catalytic activity (figure 2). The discovery of POR deficiency, in 2004,[16,17] provided an explanation for multiple hormonal deficiency, initially known as apparent combined 17OH and 21OH deficiency. Insufficient placental aromatisation of fetal androgens could contribute to the virilisation seen in some mothers carrying babies affected by POR deficiency. However, the

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	Clinical presentation	Hormonal profile	Cosyntropin stimulation testing*	Other testing
21-hydroxylase deficiency	Classic: atypical genitalia (46,XX), neonatal salt wasting (75%), and virilisation <4 year old (46,XY) Non-classic: precocious pubarche, hirsutism, oligomenorrhea/amenorrhea, and female infertility	↑ 17OHP, 21-deoxycortisol, androstenedione, and renin ↓ Cortisol and aldosterone	17OHP >30 nmol/L (>1000 ng/dL) (several times higher for classic)	Non-classic: early morning follicular phase 17OHP<6 nmol/L (<200 ng/dL) usually excludes non-classic congenital adrenal hyperplasia
11β-hydroxylase deficiency	Classic: atypical genitalia (46,XX), virilisation <4 years old (46,XY), hypertension, and hypokalaemia Non-classic: precocious pubarche, hirsutism, oligomenorrhea/amenorrhea, female infertility, and with or without hypertension	↑ DOC, 11-deoxycortisol, androstenedione and 17OHP (mild) ↓ Cortisol, aldosterone, corticosterone, and renin	11-deoxycortisol >3 times the upper limit of normal (several times higher for classic)	..
17α-hydroxylase/ 17,20-lyase deficiency	Adolescent female with absence of secondary sexual characteristics, hypertension, and hypokalaemia	↑ DOC, corticosterone (>115 nmol/L, 4000 ng/dL), and progesterone ↓ Cortisol, aldosterone, 17-hydroxypregnenolone, 17OHP, renin, DHEA, and androstenedione	Poor response of 17-hydroxypregnenolone and 17OHP Elevated ratios of DOC to cortisol and corticosterone to sex steroids	..
3β-hydroxysteroid dehydrogenase type 2 deficiency	Atypical genitalia (46,XX: rare, mild; 46,XY), neonatal salt wasting Non-classic: precocious pubarche, hirsutism, and oligomenorrhea/ amenorrhea (46,XX); atypical genitalia (46,XY; mild)	↑ 17-hydroxypregnenolone, DHEA, and renin ↓ Cortisol, aldosterone, progesterone, 17OHP, androstenedione, DOC, and 11-deoxycortisol	17-hydroxypregnenolone >150 nmol/L (5000 ng/dL) Elevated ratios pregnenolone to progesterone and 17-hydroxypregnenolone to 17OHP	Poor testosterone response hCG stimulation in infancy
P450 oxidoreductase deficiency	Atypical genitalia, with or without skeletal manifestation (Antley-Bixler), and with or without maternal virilisation	↑ Pregnenolone, progesterone, 17OHP, DOC, and corticosterone ↓ DHEA and androstenedione Variable (normal or low): cortisol, aldosterone	Variable 17OHP response, variable cortisol response (often inadequate)	Urine steroid metabolite profile shows characteristic diagnostic profile
Lipoid adrenal hyperplasia or SCC enzyme deficiency	Classic: female genitalia, neonatal salt wasting Non-classic: adrenal insufficiency (2 years to adulthood), variable gonadal function, variable genitalia (46,XY: mild)	↑ Renin ↓ All steroids Non-classic: variable	Minimal to no response Non-classic: variable response, ↓cortisol common	Classic: minimal response hCG stimulation Genetic testing needed to differentiate lipoid congenital adrenal hyperplasia and SCC deficiency

17OHP=17-hydroxyprogesterone. DHEA=dehydroepiandrosterone. DOC=deoxycorticosterone. hCG=human chorionic gonadotropin. SCC=side chain cleavage. *Administration of standard dose of 250 μg cosyntropin (in very low birthweight infants the dose may be reduced to 0·125 μg), concomitant measurement of 17OHP, cortisol, DOC, 11-DOC, 17-hydroxypregnenelone, DHEA, and androstenedione at baseline and 60 min to distinguish 21-hydroxylase deficiency from other rarer forms of congenital adrenal hyperplasia.

Table 2: **Clinical presentation and biochemical findings**

production of androgens via an alternative pathway to the one that produces the most potent androgen, non-aromatisable 5α-dihydrotestosterone, might also explain the prenatal virilisation of female patients affected by POR deficiency, while affected individuals have postnatal sex steroid deficiency.[17] POR also acts as an electron donor to cytochrome P450 (CYP) enzymes other than steroidogenic CYP enzymes, which explains POR deficiency-associated changes in drug metabolism[52] and the pathogenesis of skeletal dysplasia, which is often seen in patients.[53]

Most *POR* mutations retain some enzymatic function; homozygous mutations with complete loss of function might not be viable, as seen in rodent models.[54] Presentation of patients with *POR* mutations varies from mildly affected women with amenorrhea and polycystic ovaries or men with androgen deficiency, to severe hormone disturbances causing atypical genitalia in both 46,XX and 46,XY patients (table 1, 2). 46,XX virilisation does not progress, and patients postnatally have sex steroid deficiency. Craniosynostosis, radioulnar or radiohumeral synostosis, midface hypoplasia, and other skeletal manifestations that resemble the Antley-Bixler syndrome can occur.[16]

Generally, patients with POR deficiency do not have mineralocorticoid deficiency as impairment of 17α-hydroxylase increases production of mineral-ocorticoid intermediates, and affected adults can develop hypertension.[16,36] Patients have variable cortisol responses to cosyntropin testing, with most patients requiring either permanent or stress dose glucocorticoid coverage.[36]

Lipoid congenital adrenal hyperplasia

Classic lipoid congenital adrenal hyperplasia is characterised by deficiency of all steroid hormones and is due to *StAR* mutations (table 1, figure 2). StAR regulates the transfer of cholesterol from the outer to inner mitochondrial membrane, a key step in the initiation of steroidogenesis. When cholesterol cannot be mobilised, adrenal lipid droplets accumulate and are seen on autopsy, hence the name lipoid congenital

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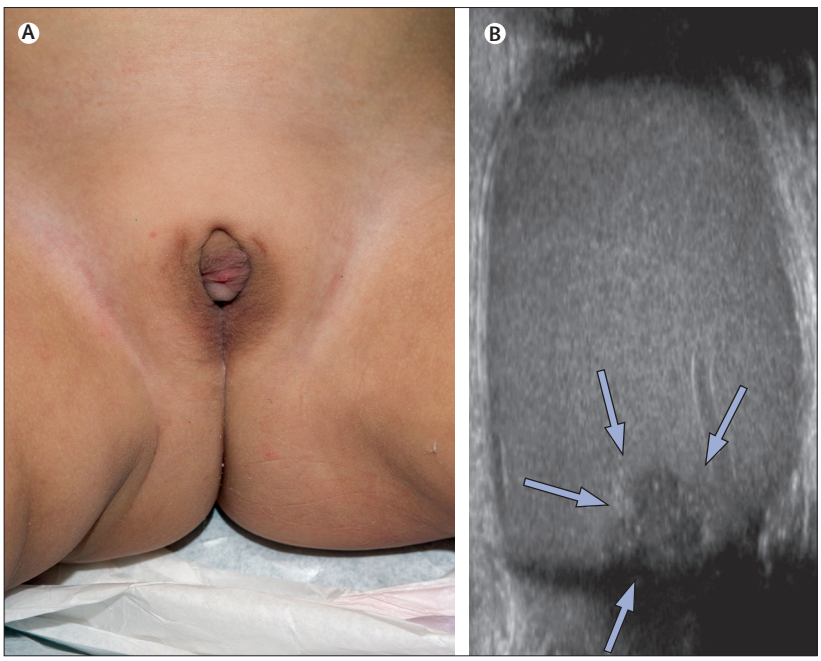

Figure 3: **Adverse outcomes in congenital adrenal hyperplasia**
(A) Atypical genitalia with clitoromegaly and posterior labial fusion of a 46,XX infant with 21-hydroxylase deficiency. (B) A right sided, lobulated echopenic focus measuring 2·7 × 1·0 x 1·1 cm, consistent with testicular adrenal rest tissue.

adrenal hyperplasia. The lipoid form is one of rarest forms of congenital adrenal hyperplasia and results in neonatal crisis and female external genitalia in both 46,XX and 46,XY infants (table 2).[55] Later presentation of lipoid congenital adrenal hyperplasia up to 1 year of age has been described.[56]

The pathogenesis of lipoid congenital adrenal hyperplasia is explained by a two-hit model: the first hit arises from the loss of StAR production, which leads to accumulation of intracellular cholesterol and cholesterol esters, and the second hit arises from destruction of cellular function by accumulated products.[55,57,58] This two-hit mechanism explains some unusual phenotypes. Spontaneous puberty has been described in 46,XX patients, caused by minimal ovarian *StAR* expression.[55] The ovaries are quiescent during fetal life and childhood and therefore toxic accumulation of cholesterol can be delayed until adolescence.

A non-classic form of lipoid congenital adrenal hyperplasia was first described in 2006,[59] and was associated with mutations that retain approximately 20–30% of StAR activity. Most of these cases were initially misdiagnosed as Addison's disease or isolated familial glucocorticoid deficiency.[60] Patients with non-classic lipoid congenital adrenal hyperplasia can present early as toddlers or later up to adulthood, with insidious onset of glucocorticoid deficiency, hyperpigmentation, and high ACTH concentrations (but mostly intact mineralocorticoid function). Wide variation in gonadal function has been reported, ranging from hypergonadotropic hypogonadism to normal gonadal function.[55] Similarly, 46,XY patients with non-classic lipoid congenital adrenal hyperplasia might have normal male genitalia and undergo normal puberty, or be born with atypical genitalia.[61]

SCC deficiency

SCC is involved in the first and rate-limiting step in the steroidogenic pathway (figure 2), encoded by *CYP11A1* (table 1), and is clinically and biochemically identical to lipoid congenital adrenal hyperplasia (table 2); however, patients typically have atrophic adrenals and gonads.[55] Less than 40 cases of SCC deficiency have been reported.

Similar to non-classic lipoid congenital adrenal hyperplasia, non-classic SCC deficiency has been described with delayed adrenal insufficiency onset and variable gonadal effect, caused by mutations that correspond to 7–30% of retained enzyme activity.[62–65]

Since StAR and SCC deficiency are similar clinically and biochemically, DNA testing is the only definitive method to distinguish between the two, with StAR deficiency being more common.

Diagnosis

Neonatal screening for 21OH deficiency is done via measurement of 17OHP concentration in dried blood spots on filter paper. Second-tier screening with liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) can efficiently measure a panel of steroids. LC-MS/MS has been used to successfully diagnose 11βOH deficiency,[66] but the focus of neonatal screening remains detection of 21OH deficiency. Premature, stressed, or ill infants could have falsely elevated 17OHP concentrations; the specificity of diagnosis is improved with gestational age stratification.[67] Tests that make use of 21-deoxycortisol, which is elevated in 21OH deficiency, might increase neonatal screening specificity.[68]

If an infant tests positive for 21OH deficiency in a neonatal screen or is clinically suspected of having congenital adrenal hyperplasia (ie, ambiguous genitalia), confirmatory testing is indicated. Although a baseline panel of LC-MS/MS steroids can be diagnostic for 21OH deficiency, its diagnosis often requires cosyntropin testing[23,69] and is based on a characteristic rise in adrenal hormones preceding the enzymatic blockage (table 2). The fact that 17OHP concentration might be elevated in other types of congenital adrenal hyperplasia, such as 11βOH or POR deficiency, should also be considered. An alternative approach to serum steroid analysis is urinary steroid profiling, which captures the entire steroid metabolome.[70] Additional tests and genotyping might be needed to confirm the diagnosis.

21OH deficiency screening after infancy relies on the measurement of early morning (before 0800 h) 17OHP concentration. A 17OHP concentration above 30 nmol/L (1000 ng/dL) is diagnostic for 21OH deficiency, although a random concentration of 303 nmol/L

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(10 000 ng/dL) or greater is commonly observed in the classic form (table 2).[23] A 17OHP concentration of less than 6 nmol/L (200 ng/dL) usually excludes non-classic congenital adrenal hyperplasia if 17OHP is measured during the follicular phase of a reproductive-age woman.[71] Cosyntropin stimulation testing is often needed for diagnosis of the non-classic form.

The diagnosis of POR deficiency can be best made with a urinary steroid profile which reveals characteristic precursor accumulation that can be captured by steroid ratios,[36] whereas serum steroid analysis often yields confusing results because of the overlapping effects of combined 17OH and 21OH deficiency. Further criteria for urinary and serum metabolites have been suggested to diagnose POR deficiency prenatally or differentiate POR deficiency from 21OH deficiency.[72,73]

Management of congenital adrenal hyperplasia

Medical treatment

Glucocorticoid therapy

The mainstay of treatment in the classic forms of congenital adrenal hyperplasia is chronic glucocorticoid therapy (panel). Because of their growth-suppressing effect, long-acting glucocorticoid treatment is avoided in children, but is sometimes used in adults.[75] The goal of glucocorticoid therapy is to optimise control of excess hormones, replace deficient hormones, and avoid potential Cushingoid side-effects. Laboratory results should guide but not define management; clinical evaluation should always be considered.

In general, higher doses of glucocorticoids are needed to achieve adequate suppression of hormone excess (ie, androgens in the virilising forms of congenital

Panel: **Management of congenital adrenal hyperplasia**

Glucocorticoid replacement

- Needed in classic forms of congenital adrenal hyperplasia, variable use in non-classic forms and P450 oxidoreductase deficiency
- Children: hydrocortisone (8–15 mg/m² per day) divided into three doses where the lowest dose is used to allow normal growth while controlling adrenal steroids[23,74]
- Adolescents and adults: hydrocortisone 2–3 times daily or longer-acting[23,74] glucocorticoids, such as prednisone (5·0–7·5 mg per day; one or two times daily), prednisolone (3–7 mg per day; one or two times daily), or dexamethasone (0·25–0·5 mg per day; once daily)
- Monitor for over-replacement: weight gain, central obesity, striae, stunted growth (children), decline in bone mineral density
- Monitor for under-replacement: weight loss, fatigue, hyperandrogenism (21-hydroxylase [21OH] and 11β-hydroxylase [11βOH] deficiency), hypertension (11βOH, 17-hydroxylase [17OH] deficiency, and in adult patients with P450 oxidoreductase [POR] deficiency)
- In women, monitor for cycle regulation and, if appropriate, anovulation
- In males, monitor for testicular adrenal rest tissue (TART) using testicular ultrasound from adolescence onward; if positive, then offer sperm count and motility assessment and counsel regarding the possibility of cryopreservation of semen

Stress dosing

- Needed if patient receiving glucocorticoid therapy or cortisol response to cosyntropin stimulation <500 nmol/L (18 mg/dL)[23,74]
- Double or triple glucocorticoid dose during intercurrent illness (fever, gastrointestinal illness), surgery, or trauma
- Intramuscular or subcutaneous hydrocortisone if unable to take oral glucocorticoid (home regimen). Children 50 mg/m²; adults 100 mg intravenous bolus followed by 200 mg over 24 h (hospital regimen)[74]

Mineralocorticoid replacement

- Needed in salt-wasting forms of congenital adrenal hyperplasia
- Fludrocortisone 50–200 µg daily to achieve a plasma renin activity in the mid–normal range[23,74]
- First 6–12 months of life: sodium chloride 1–2 g (17–34 mmol/L) daily, divided and given with feeds[23]
- Monitor for over-replacement: hypertension, oedema, and suppressed plasma renin activity
- Monitor for under-replacement: salt-craving, orthostatic hypotension, and elevated plasma renin activity
- Encourage salt intake during hot weather and conditions that promote excessive sweating. Consider seasonal adjustment of fludrocortisone dose in countries with very hot summers

Sex steroid replacement

- Needed in forms of congenital adrenal hyperplasia that result in sex steroid deficiency
- For pubertal females, oral oestradiol (0·5 mg per day advanced to 1–2 mg per day); or transdermal (25 µg per day advanced to 75–100 µg per day) over 2–3 years; progesterone added following 2 years of oestrogen monotherapy or when breakthrough bleeding occurs, 100–200 mg per day, or medroxyprogesterone acetate 5–10 mg per day, or norethindrone acetate 2·5–5 mg per day, for 5–10 days, in women with intact uterus[35]
- For pubertal males, intramuscular testosterone (50 mg per month titrated to about 200 every 2 weeks) or transdermal testosterone (titrated to 25–100 g per day)[35] is indicated

Anti-hypertensive treatment

- Needed if glucocorticoid unsuccessful in treatment of hypertension in 11βOH and 17OH deficiency
- Spironolactone 50–200 mg per day in one or two divided doses or eplerenone 50–100 mg per day

(Panel continues on next page)

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(Panel continued from previous page)

- Calcium-channel blockers, such as amlodipine, 2·5–10 mg per day, can be used

Anti-androgen treatment

- Oral contraceptives with or without spironolactone to control hirsutism, and amenorrhea in non-classic 21OH and 11βOH deficiency

Infertility

- Initiate glucocorticoid for non-classic forms 21OH and 11βOH deficiency
- Optimise glucocorticoid therapy with suppression of follicular phase progesterone (females) and shrinkage of TART (males) for 21OH and 11βOH deficiency
- Clomiphene citrate stimulation with progesterone supplementation for hypogonadal forms of congenital adrenal hyperplasia
- Consider in-vitro fertilisation (females) or intra-cytoplasmic sperm injection (males)

Pregnancy

- If patients are on glucocorticoid therapy, hydrocortisone, prednisone, or prednisolone can be used— dexamethasone should be avoided
- Increase glucocorticoid dose by 20–40%, particularly during third trimester[74]
- Stress dosing for labour and delivery

Additional monitoring requirements

- Clinical evaluation frequently in first year of life, every 4–6 months for growing child and yearly for adults
- Patients on glucocorticoid replacement should wear an emergency bracelet or card, receive sick day rule education, and carry an emergency hydrocortisone kit
- Screening for psychological and sexual health issues and late-onset complications of genital surgery, if indicated
- Age-appropriate vitamin D and calcium intake and bone mineral density screening during early adulthood
- Orthopaedic management may be needed for POR deficiency

adrenal hyperplasia, classic 21OH and 11βOH, or deoxycorticosterone in 17OH deficiency), than doses of glucocorticoids given for replacement purposes when all all steroids are deficient. Low glucocorticoid doses can also be used in the non-classic forms of congenital adrenal hyperplasia, if treatment is indicated.[76]

For women planning to conceive, a glucocorticoid that does not reach the fetus and is inactivated by placental 11βHSD2, such as prednisone, prednisolone, or hydrocortisone, is typically used and continued throughout pregnancy.[23]

Patients with non-classic congenital adrenal hyperplasia are treated according to their symptoms. Children with non-classic 21OH deficiency should be treated if they have progressive signs and symptoms of virilisation with advanced skeletal maturation. Women with non-classic congenital adrenal hyperplasia with signs of androgen excess can often be successfully treated with oral contraceptives, and if needed, in combination with spironolactone. Glucocorticoid therapy is used for female infertility in non-classic 21OH deficiency. Furthermore, a reduction in miscarriage rate has been reported when glucocorticoids are taken throughout pregnancy.[77,78]

Mineralocorticoid replacement

Mineralocorticoid, in the form of fludrocortisone, is given to achieve a plasma renin activity in the healthy range in salt-wasting forms of congenital adrenal hyperplasia (panel).[23] Mineralocorticoid dose is independent of body surface area, although higher doses are usually needed during the first 6 months of life because of neonatal physiological mineralocorticoid resistance.[79] Infants during the first year of life also require salt supplementation. Although patients with simple virilising 21OH deficiency have some aldosterone production, relative aldosterone insufficiency exists and fludrocortisone is recommended because it allows for glucocorticoid reduction, which leads to improved height outcomes.[80]

Glucocorticoid stress dosing

Patients receiving glucocorticoid treatment, including those with non-classic congenital adrenal hyperplasia, need to be educated on adrenal crisis prevention and the necessity of increasing glucocorticoid dose during intercurrent illness (panel). Intramuscular, subcutaneous, or intravenous hydrocortisone should be given to patients when oral intake is not possible, and stress dose management is identical to that recommended in primary adrenal insufficiency.[74] Patients with classic 21OH deficiency also have epinephrine deficiency, due to abnormal adrenomedullary formation;[81] this places patients at risk for hypoglycaemia, especially when fasting, or during acute illness. Adrenomedullary function has not been studied in the rarer forms of congenital adrenal hyperplasia.

Patients with non-classic congenital adrenal hyperplasia can have suboptimal cortisol response on cosyntropin stimulation testing (<18 µg/dL of cortisol). If patients are

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asymptomatic, daily glucocorticoid use is not indicated, but glucocorticoid stress coverage should be used during serious illness or major surgery.[74]

Sex steroids

Sex steroid replacement is initiated around the time of physiological puberty in patients with 17OH deficiency,[35] 3βHSD2 deficiency,[48] lipoid congenital adrenal hyperplasia, SCC deficiency,[55] or POR deficiency[82] (as needed). Replacement of androgen (in men) and oestrogen (in women), with progestin to induce cyclical bleeding (if uterus is present), are advanced slowly to adult regimens (panel).

Anti-hypertensives

In both 11βOH and 17OH deficiency, glucocorticoid therapy is often sufficient to control hypertension by suppressing deoxycorticosterone. However, because high dose glucocorticoid therapy and complete suppression of the hypothalamic-pituitary-adrenal axis should be avoided, deoxycorticosterone is not fully suppressed and many patients eventually become hypertensive. In such cases, a mineralocorticoid receptor antagonist or calcium channel blocker can be used to treat hypertension (panel).[35,83]

Controversial therapies

Genital surgery

Genital surgery for patients with disorders of sex development is a complex issue that has generated much controversy. Historically, surgeons have recommended surgery on the basis of genital appearance and fertility potential. In the past two decades, some advocacy groups and physicians have recommended delaying surgery so that patients can participate in the decision regarding surgical intervention. Conversely, others have expressed concern about the puacity of outcome data and psychosocial stress resulting from not doing early surgery.[84] Most importantly, the patient's family should always be educated on the advantages and disadvantages of having and not having surgery. An interdisciplinary team of specialists is often required to navigate the decision-making process.[85]

An international group of experts, appointed by the Endocrine Society to develop clinical practice guidelines for congenital adrenal hyperplasia due to 21OH deficiency, concluded that surgery should be considered for considerably virilised 46,XX patients.[23] The timing of surgery is beyond the scope of this Seminar but options include a one-stage approach—ie, simultaneous neurovascular-sparing clitoroplasty, labioplasty, and vaginoplasty—done in infancy (the standard option in many countries including the USA and UK)[23,86,87] or delayed until puberty, or a two-stage approach with labioplasty and clitoroplasty done in infancy and vaginoplasty delayed until puberty.[86,87] Most patients with congenital adrenal hyperplasia caused by 21OH deficiency prefer early surgery.[88] Although in-utero exposure to androgens has been shown to affect behaviour, with male typical behaviour patterns commonly seen in 46,XX patients with classic congenital adrenal hyperplasia, gender dysphoria is extremely rare and the recommended sex assignment of 46,XX patients with disorders of sex development due to congenital adrenal hyperplasia is female.[85]

The main challenge of surgery for the 46,XX virilised patient with congenital adrenal hyperplasia is the imperfect functional and cosmetic outcomes, including urinary incontinence, vaginal stenosis, and clitoral pain, all of which can affect psychosocial and sexual wellbeing.[86] Many of the new surgical approaches have not existed for long enough to assess outcomes. Patients should be referred to a specialist surgeon with experience managing disorders of sex development.

Surgical reconstruction of 46,XY atypical genitals is complex. Chordee repair and surgery for distal hypospadias have high success rates,[87] but proximal hypospadias repair is more challenging, with higher complication and reoperation rates than distal hypospadias repair. The main complications are urethral stricture, meatal stenosis, urethrocutaneous fistula, and glans wings separation.[87]

Early gonadal neoplastic changes were observed histologically as early as 1 year of age in a 46,XY patient with classic lipoid congenital adrenal hyperplasia.[89] Gonadectomy is recommended in 46,XY patients raised as female who are severely affected, although the risk of gonadal malignancy is unknown.

Prenatal treatment

For over 30 years dexamethasone was offered to pregnant women at risk of having a child with classic virilising congenital adrenal hyperplasia, which aimed to suppress fetal androgen production and reduce virilisation of females affected by congenital adrenal hyperplasia.[90] Dexamethasone, unlike hydrocortisone and prednisolone, crosses the placental barrier to the fetus without inactivation. Prenatal therapy is controversial because only one in eight fetuses will be female with congenital adrenal hyperplasia when both parents are carriers. Long-term effects of in-utero dexamethasone exposure are unknown, and potential effects on the brain, behaviour, and cognition of fetuses have been described.[91–94]

Testing of fetal cells present in maternal circulation for congenital adrenal hyperplasia is being studied to avoid 46,XY treatment and initiate early treatment in affected 46,XX patients.[95] Cell-free fetal DNA obtained from mother's plasma as early as 5 weeks gestation has correctly identified fetal congenital adrenal hyperplasia status in 14 families.[96] Multiple international groups, including medical societies in the USA and Europe, have stated that prenatal therapy should only be considered in a research setting with full disclosure of potential risks and benefits.[23,97] Long-term effects of prenatal dexamethasone

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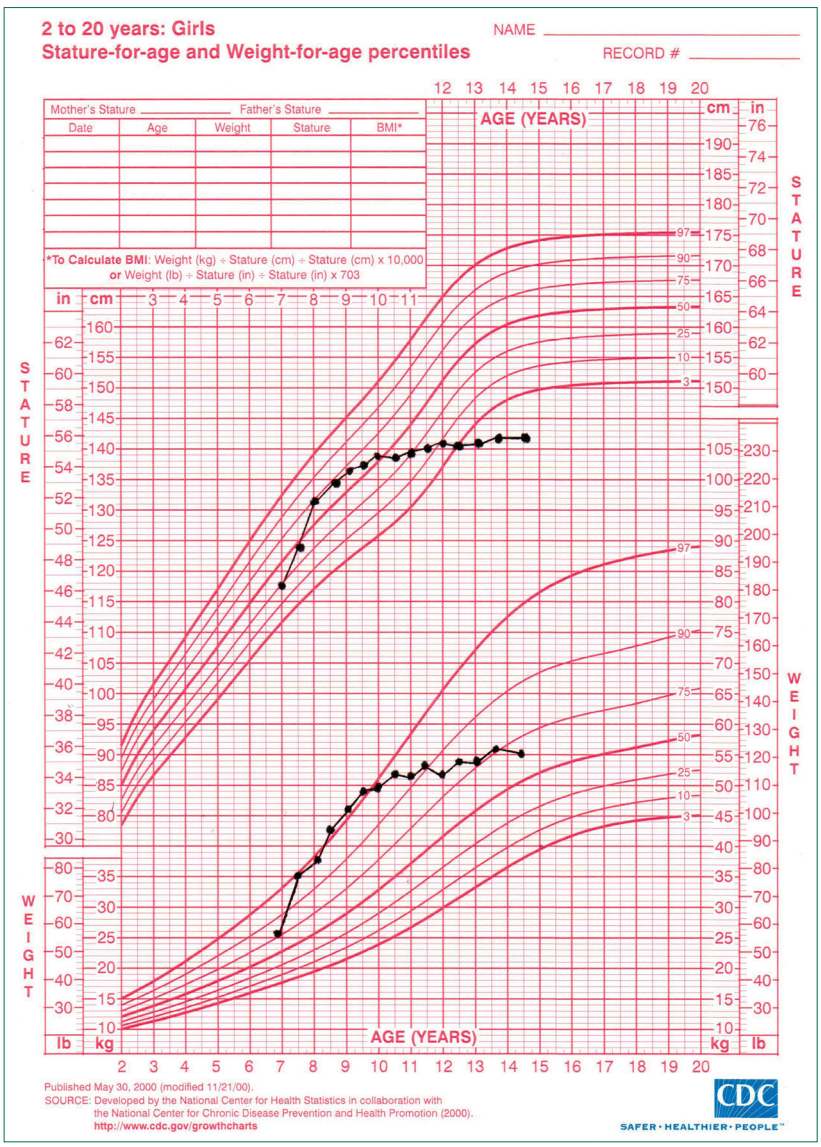

Figure 4: **Growth chart of a female patient with classic 21-hydroxylase deficiency**
The patient experienced early puberty and epiphyseal fusion of her bones due to excess adrenal sex steroids, and obesity due to excess glucocorticoid therapy. Both probably contributed to her adult short stature.

exposure requires further study but early non-invasive fetal DNA testing would potentially restrict exposure to female fetuses affected by congenital adrenal hyperplasia.

Bilateral adrenalectomy

Bilateral adrenalectomy has been used successfully to treat female infertility with uncontrolled hyperandrogenism in patients with 21OH deficiency[98] and uncontrolled hypertension in patients with 11βOH deficiency.[99] Although follow-up of patients who have undergone an adrenalectomy is positive overall, these patients appear to be at increased risk of adrenal crisis and about a third develop adrenal rest tissue if their glucocorticoid dose is too low.[100] Adrenalectomy should only be considered in patients in whom all available medical interventions have failed.

Long-term complications

Glucocorticoid deficiency is characteristic of the severe forms of congenital adrenal hyperplasia and is potentially life threatening. In a study[101] in Sweden, 588 patients with congenital adrenal hyperplasia were compared with a national population-based registry, which revealed excess mortality in patients with congenital adrenal hyperplasia due to adrenal crises, highlighting the importance of this aspect of the disease. Results from a cross-sectional questionnaire-based study[102] of 122 patients with congenital adrenal hyperplasia showed that most adrenal crises occurred during infancy, with a second peak in crises occurring around late adolescence, and were precipitated mainly by respiratory and gastrointestinal infections.

All children with congenital adrenal hyperplasia who are receiving glucocorticoid therapy are at risk of growth impairment and short stature. The effect of glucocorticoids on growth is dose-dependent,[103] thus management always should aim to treat children with the lowest possible effective dose of glucocorticoids. Alterations in sex steroid exposure can also influence height. Late puberty can occur in patients with the rare types of congenital adrenal hyperplasia associated with sex steroid deficiency and can enhance adult height; conversely, exposure to excess androgens and oestrogens in the virilising types of congenital adrenal hyperplasia can result in early puberty and epiphyseal fusion (figure 4).[80] In a meta-analysis[80] of 35 studies of patients with classic 21OH deficiency, these patients had an average final height 1·38 standard deviations below the normal population range. Whereas studies[104,105] reveal an association between higher doses of hydrocortisone and shorter final patient height, earlier rather than later diagnosis and treatment of classic 21OH deficiency has been associated with improved height outcomes,[106] emphasising the importance of hyperandrogenism prevention.

Cardiovascular disease risk factors commonly coexist with congenital adrenal hyperplasia. In a cross-sectional study[107] of patients in the UK with classic 21OH deficiency, more than half of female patients were obese and a third had insulin resistance. In a cohort of 588 patients in Sweden with congenital adrenal hyperplasia, prevalence of hypertension, hyperlipidaemia, diabetes, and venous thromboembolism were higher than in controls.[108]

Long-term glucocorticoid exposure, particularly at the higher doses used to achieve tight control, is one of the main risk factors for compromised bone health. Data from studies over the past two decades show lower bone mass density in patients with 21OH deficiency than in control populations, with the prevalence of low bone mass density (osteoporosis or osteopenia) ranging from 37% to 81%,[107,109–111] and some studies[109,112] reporting an increased fracture rate.

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Both male and female patients with the hypogonadal forms of congenital adrenal hyperplasia have infertility. However, one woman with classic lipoid congenital adrenal hyperplasia had a successful pregnancy with clomiphene citrate stimulation followed by progesterone supplementation.[113] In-vitro fertilisation and transfer of cryopreserved embryos has successfully resulted in a live birth in a patient with lipoid congenital adrenal hyperplasia and 17OH deficiency.[114,115] Patients with *POR*, *StAR*, and *CYP17A1* mutations might also have ovarian cysts and cyst torsion.[116–118]

In the virilising forms of congenital adrenal hyperplasia, excess adrenal sex steroids can lead to hypogonadotropic hypogonadism[119,120] and increased progesterone can interfere with endometrial implantation.[121,122] Optimising glucocorticoid management might resolve hypogonadotropic hypogonadism and endometrial implantation interference and suppression of follicular phase progesterone enhances the likelihood of ovulation and subsequent conception.[123,124]

A main cause of male infertility in patients with classic 21OH and 11βOH deficiency is presence of adrenal rest tissue. Adrenal rest tissue is thought to arise from aberrant cells of adrenocortical origin that migrate during fetal development along with the gonads after the adrenal and gonadal cells separate from the urogenital ridge.[125] Adrenal rest tissue is most commonly found in the rete testis (figure 3B) and has been described in the ovaries and broad ligament.[126,127] Testicular adrenal rest tissue (TART) causes obstructive azoospermia and deficient spermatogenesis.[125] Low inhibin B concentrations reflect the decline of Sertoli cell function and can be used to monitor it.[119] 44–94% of men[111,120,128,129] and 21–33% of boys[111,130] with classic 21OH deficiency have TART; which has also been reported in male patients with 11βOH and HSD3B2 deficiency,[131–133] and rarely in non-classic congenital adrenal hyperplasia.[128] TART shrinkage and reversal of infertility in patients is possible with glucocorticoid therapy;[134] however, therapy effectiveness is variable because non-reversible fibrotic changes can occur over time.[125]

When infertility reversal and TART shrinkage are unsuccessful, other treatment methods such as intracytoplasmic sperm injection could be considered.[135] Testis-preserving surgery with TART resection has not restored fertility in male patients with congenital adrenal hyperplasia,[136] but has been successful in patients with orchialgia where simultaneous intraoperative sperm retrieval was reported.[137]

Future directions

Alternative androgen synthesis pathways

The quest for new and improved biomarkers of disease severity or treatment response in congenital adrenal hyperplasia has included exploration of alternative androgen synthesis pathways. The so-called backdoor pathway leads to synthesis of 5α-dihydrotestosterone, without dehydroepiandrosterone, androstenedione, and testosterone as intermediates, originating directly from 17OHP (figure 2). This pathway has been implicated in the normal development of male genitalia[61] and the prenatal virilisation of female patients with congenital adrenal hyperplasia.[17] Accumulation of 17OHP, as observed in 21OH and POR deficiency, increases the substrate flow to the backdoor pathway and results from subsequent studies have shown increased alternative pathway metabolite excretion in patients with congenital adrenal hyperplasia due to POR[138] and 21OH deficiency.[139]

Another androgen synthesis pathway involves the generation of 11-oxygenated C19 steroids in the adrenal cortex via CYP11B1 activity (figure 2),[140] including 11-ketotestosterone and 11-keto-5α-dihydrotestosterone, which are androgens that bind and activate the androgen receptor.[141,142] 11-oxygenated C19 steroids are increased in congenital adrenal hyperplasia due to 21OH deficiency [143,144] and exaggerated activity of both backdoor and 11-oxygenated C19 pathways persists in treated patients, even if the activity of the classic androgen pathway activity is downregulated.[143] Insights into these novel steroid markers will help to improve monitoring tools and define treatment targets.

Genetic advances

Genetic studies of congenital adrenal hyperplasia have provided insight into the pathophysiology and subtle clinical aspects of the disease. Initially described in 1989,[145] the *TNXB* gene, which encodes tenascin-X—a glycoprotein expressed in connective tissue—and its highly homologous pseudogene *TNXA*, flank *CYP21A2* and its pseudogene *CYP21A1P*, respectively. The identification of chimeric genes that impair both the *CYP21A2* and *TNXB* genes, explained an unusual observed phenotype of connective tissue dysplasia, consistent with hypermobility-type Ehlers Danlos syndrome, in patients with 21OH deficiency.[146,147] This novel syndrome, congenital adrenal hyperplasia-X, was prevalent in 8·5 % of a cohort of 246 unrelated patients with 21OH deficiency.[148]

Apart from mutations in genes that cause congenital adrenal hyperplasia, other genes can modify steroid action, salt balance, or androgen sensitivity and affect phenotype.[149–151]

Genotyping is essential for confirming carrier state, and is useful for genetic counselling or establishing the diagnosis of a patient who cannot undergo accurate hormonal testing due to glucocorticoid therapy. Genotyping might one day help to predict future outcomes and be efficacious in screening programmes.[152]

Novel therapies

Most adverse outcomes in patients with congenital adrenal hyperplasia are attributable to hormonal imbalances or treatment-related comorbidities. Development of new and improved therapies that target different aspects of the pathophysiology of congenital adrenal hyperplasia is

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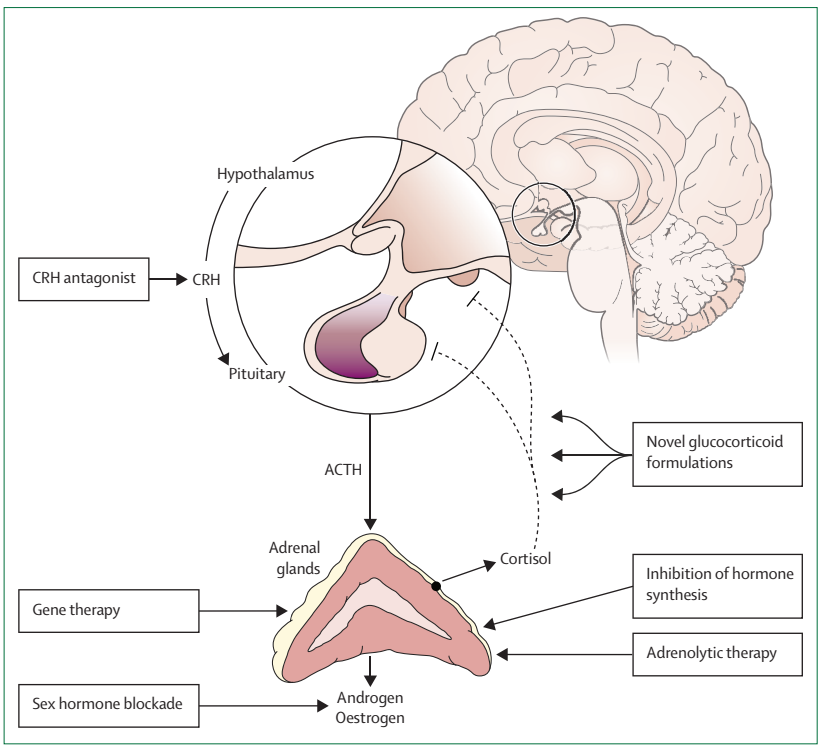

Figure 5: **Novel and emerging treatments for the management of congenital adrenal hyperplasia**
These approaches target various aspects of the hypothalamic-pituitary-adrenal axis and steroid production. CRH=corticotropin-releasing hormone. ACTH=adrenocorticotropic hormone.

ongoing (figure 5) and their efficacies for the treatment of classic 21OH deficiency are being studied.

One therapeutic approach is to replace cortisol in a physiological manner. Circadian cortisol replacement might achieve improved ACTH control and thus adrenal steroid secretion. A modified-release oral hydrocortisone preparation successfully lowered androgen levels in patients and decreased the hydrocortisone equivalent dose by use of a twice-daily regimen in a phase 2 study of 16 patients with classic 21OH deficiency.[153] A phase 3 study is currently underway (NCT02716818). Continuous subcutaneous hydrocortisone infusion via an insulin pump mimicking cortisol circadian rhythm, has similarly shown adequate ACTH suppression in patients with lower total hydrocortisone doses compared with conventional treatment,[152–155] and improved quality-of-life and decreased fatigue in eight patients with classic 21OH deficiency.[155] Long-standing comorbidities, such as insulin resistance and TART, remained mostly unchanged after 6 months, suggesting that early intervention is key and other approaches might be needed to treat well established comorbidities.

Because ACTH is the primary driver for excess steroid accumulation, strategies for reducing ACTH are being investigated. A phase 1 proof-of-principle study[156] with a corticotropin-releasing factor type 1 receptor antagonist, lowered morning ACTH or 17OHP concentrations in six of eight female participants with classic 21OH deficiency after a single dose. Future multidose trials are needed.

Pharmacological blockade or inhibition of sex steroid synthesis in prepubertal children or women receiving sex hormone replacement therapy would allow for lower dose glucocorticoid replacement in the virilising forms of congenital adrenal hyperplasia. This approach was studied in 28 prepubertal children with classic 21OH deficiency by use of an anti-androgen and aromatase inhibitor in combination with lower dose hydrocortisone and fludrocortisone, and was successful in normalising growth over 2 years.[157] Pharmacological inhibition of sex steroid synthesis was also tested in adult women with congenital adrenal hyperplasia receiving gonadal hormone replacement in a 6 day phase 1 dose-escalation study of abiraterone, a potent CYP17A1 inhibitor.[158] Promising results were reported when androstenedione concentrations normalised in five of six women after abiraterone was added to physiological doses of glucocorticoid and fludrocortisone.[158] Pharmacological inhibition of sex steroid synthesis is also being studied with an inhibitor of acyl-coenzyme A:cholesterol-O-acyltransferase 1 (NCT02804178) in a phase 2 study of classic 21OH deficiency.[159]

Adrenal enzyme inhibitors with adrenolytic properties might be useful in the treatment of congenital adrenal hyperplasia. Mitotane inhibits CYP11B1 and CYP11A1, and is adrenolytic with longer term use. Mitotane was successfully used to shrink TART and restore fertility in a 29-year-old man with classic 21OH deficiency.[160] However, due to the multiple toxic effects of mitotane, the development of alternative adrenolytic therapies is needed.

Congenital adrenal hyperplasia is a monogenic disease, so gene therapy with cell-based and gene-editing technologies might be able to restore defective steroidogenesis.[161] Adrenal transplantation with novel technology that uses bovine adrenocortical cells has been successful in animal models of adrenal insufficiency.[162] Future technological and genetic advances might enable a cure to congenital adrenal hyperplasia.

Conclusion

Congenital adrenal hyperplasia is a group of rare diseases that can result in high morbidity and mortality if left undiagnosed and untreated. The identification of alternative adrenal biomarkers has provided insight into the origin and synthesis of steroid production and has the potential to alter disease management. Decades of progress in understanding the genetics and pathophysiology of the various forms of congenital adrenal hyperplasia have led to a recent explosion in the investigation of new and improved therapies that promise to improve patient outcomes.

Contributors
DPM conceived the framework for the Seminar, wrote the Controversial therapies and Future directions sections, contributed to the writing and editing of all sections and figures, and coordinated oversight of the final manuscript. DE-M wrote the first versions of the manuscript, created the figures, and did most of the scientific literature searches. WA wrote the

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Alternative androgen synthesis pathways section and contributed to the writing and editing of all sections and figures. All authors did several rounds of amendments and have seen and approved the final text.

Declaration of interests

WA reports licensing of a patent by Alta Biosciences, research grants from Diurnal and Millendo, scientific consultancy fees from Bayer AG, and a patent pending for a computational algorithm for rapid interpretation of steroid data pending. DPM received research funds from Diurnal and Millendo Therapeutics through the National Institutes of Health Cooperative Research and Development Agreement. DE-M declares no competing interests.

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