MANAGEMENT OF ENDOCRINE DISEASE

Diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency

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Abstract

Non-classic congenital adrenal hyperplasia (NCAH) is a relatively common disorder regardless of ethnicity, but most cases are never diagnosed, especially in males. A baseline 17-hydroxyprogesterone measurement may be used for screening, but 17-hydroxyprogesterone measurement after ACTH stimulation is the gold standard. We advocate a *CYP21A2* mutation analysis to verify the diagnosis, for genetic counselling and for better prognostic and treatment guidance. Most patients are diagnosed in adolescence and adult life with hirsutism, acne, a PCOS-like picture and fertility issues. Many men with NCAH never seek medical attention and escape diagnosis. Although treatment is somewhat controversial, an early diagnosis and start of treatment may have positive implications on growth and be relevant for preventing and ameliorating the symptoms and consequences of androgen excess that develop over time, including fertility issues. Long-term treatment with glucocorticoids will improve the androgen symptoms but may result in long-term complications, such as obesity, insulin resistance, hypertension, osteoporosis and fractures. The glucocorticoid doses should be kept low. However, complications seen in NCAH, assumed to be caused by the glucocorticoid treatment, may also be associated with long-term androgen exposure. Oral contraceptive pills are a common treatment option for young females with NCAH. Regular clinical monitoring to improve the clinical outcome is recommended. It is important to acknowledge that glucocorticoid treatment will lead to secondary cortisol insufficiency and the need for stress dosing. Studies focusing on the specific difficulties patients with NCAH face, both those with a late clinical diagnosis and those with a neonatal diagnosis obtained by screening, are warranted.

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Invited author's profile

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Introduction

Non-classic congenital adrenal hyperplasia (NCAH) is an autosomal recessive disorder caused by a deficiency of one of the enzymes involved in adrenal steroid synthesis. Deficiency of the 21-hydroxylase is by far most common. NCAH typically has 20–70% residual 21-hydroxylase enzyme activity (1) and therefore results in a less severe phenotype than classic CAH (Fig. 1). The enzyme deficiency may lead to a mild cortisol deficiency and, subsequently, to a reduced feedback inhibition on the pituitary with increased ACTH production and excess androgen synthesis as the result (2, 3). The increased ACTH drives adrenocortical growth and hyperplasia of the adrenals. Accumulation of the steroid precursors before the enzymatic block, as described above or because of enzyme kinetics, and their metabolism in the different androgen pathways result in the increased androgen synthesis and the clinical symptoms (Fig. 2). The metabolite just before the 21-hydroxylase enzymatic step, 17-hydroxyprogesterone (17OHP), is used as an indicator of the disease.

The aldosterone production required for normal electrolyte homeostasis is 100 times lower than the cortisol production rate, which means that individuals with NCAH typically do not develop salt crises, in contrast to the situation for patients with classic CAH. In addition, local cortisol production in the adrenal cortex is required for an adequate adrenomedullary organogenesis and epinephrine/adrenaline production. A correlation with the severity of epinephrine production and the different classic CAH genotype groups has been demonstrated in both children and adults (4, 5), but the adrenomedullary function in NCAH was not significantly different from that in normal controls (6). Hence, individuals with NCAH should not be at increased risk of developing hypoglycaemia (7, 8).

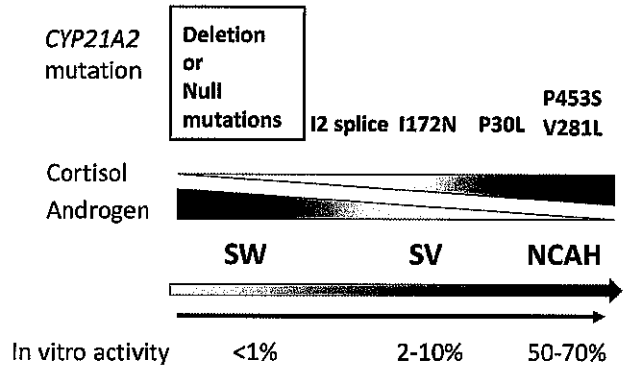

Figure 1

Severity of the different *CYP21A2* mutations in relation to the enzyme activity and the resulting clinical severity of cortisol deficiency and androgen excess. The less severe allele determines the disease severity. Mutations resulting in completely abolished enzyme activity (null mutations) and the I2 splice mutation (I2G) typically result in SW CAH and I172N in SV CAH while V281L is the most common mutation in NCAH.

This review is based on articles identified in PubMed published up to August 2018, using the search terms non-classic/nonclassical congenital adrenal hyperplasia and/or 21-hydroxylase deficiency/*CYP21A2* and late-onset CAH. Articles retrieved in the initial search were also reviewed for additional references. We focus on NCAH owing to 21-hydroxylase deficiency: clinical presentation, diagnosis, treatment and clinical outcomes: more specifically, fertility, pregnancies, bone health, mortality, cardio-metabolic disorders, tumours, voice, quality of life and psychiatric morbidity. However, most studies include both classic CAH and NCAH patients or focus on classic CAH patients, and only a few include only NCAH. Data from studies on classic CAH are presented when assumed to be of interest and similar to NCAH, but we have attempted to separate NCAH and classic CAH.

Classification and genetics

CAH is clinically classified into the classic form, which is subdivided into salt-wasting (SW) and simple virilising (SV) CAH, and the non-classic or late-onset CAH (NCAH) (9, 10). Untreated infants with SW CAH will develop a potentially lethal salt crisis in the neonatal period and both SW and SV CAH cause prenatal virilisation of external genitalia in 46,XX foetuses. NCAH does not cause prenatal virilisation; instead, according to the original clinical definition, the first symptoms should occur after 60 months of age.

The molecular genetics for 21-hydroxylase deficiency has been extensively studied. The gene for 21-hydroxylase, *CYP21A2*, is a complicated gene located close to the HLA region on chromosome 6 in tandem with a pseudogene, *CYP21A2P*, with 98% homology with the active gene, but inactive due to a number of mutations (11, 12, 13, 14, 15). The fact that more than 90% of the mutations identified in patients with CAH are picked up from the pseudogene by crossing over or gene conversion has resulted in a limited number of mutations comprising the vast majority of the patients. In fact, ten mutations and deletion represent more than 90% of the patients, which enables genotype/

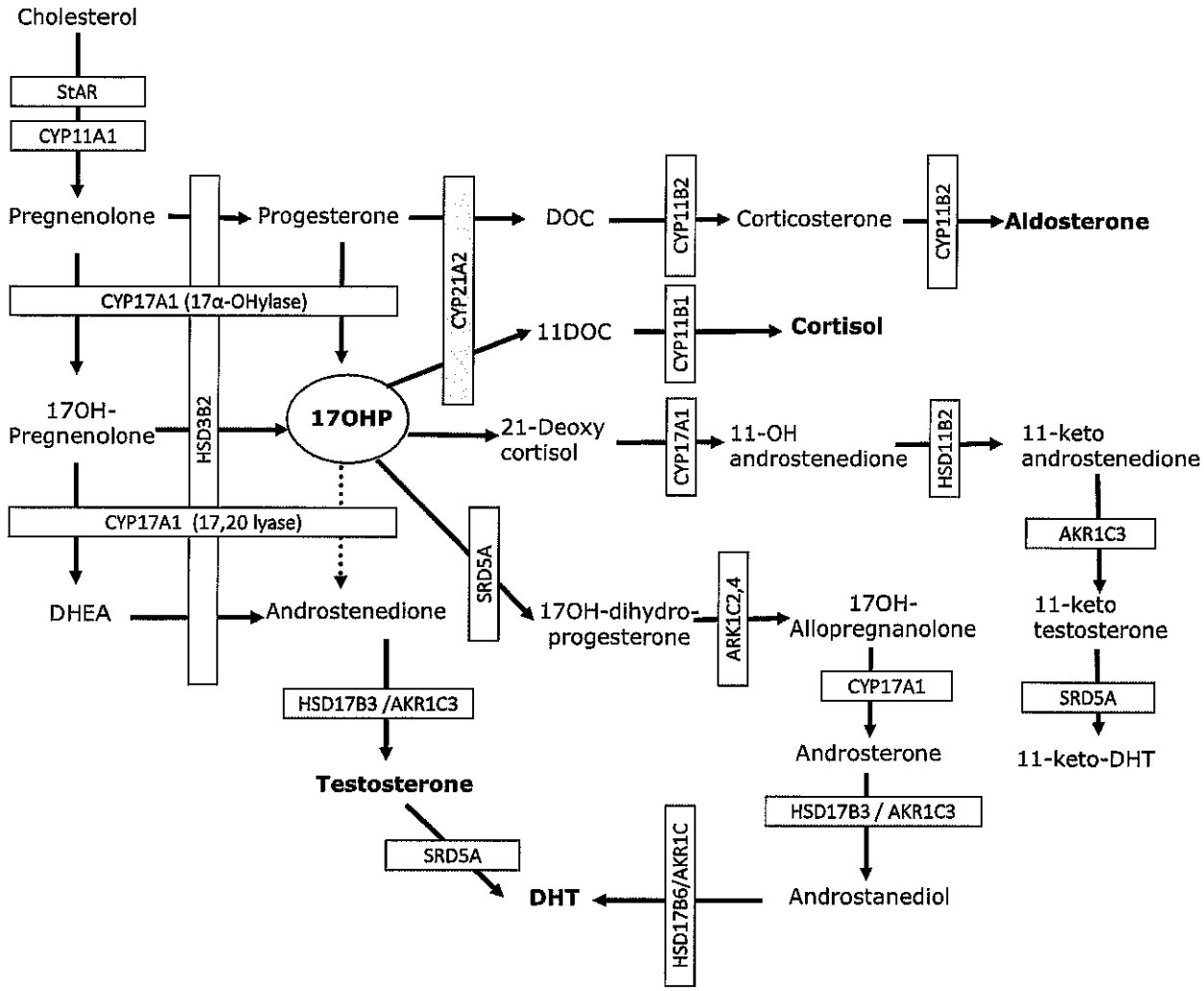

Figure 2

Schematic overview of the steroid hormone synthesis from adrenal androgens and from 17OHP in individuals with *CYP21A2* deficiency. The CYP21A2 which is deficient in CAH is depicted in grey. The subsequent increase in 17-OHP leads to increased synthesis of testosterone via androstenedione and the synthesis of dihydrotestosterone (DHT) via the 'Back door pathway'. In CYP21A2 deficiency, 17OHP is converted to 21-deoxycortisol, by the 11β-hydroxylase activity of CYP11B1, which then may be converted to the 11oxygented steroids, 11-ketotestosterone and 11-keto-DHT in peripheral tissues. 11DOC, 11-deoxycorticosterone; AKR1C3, aldo-keto-reductase 1C3; CYP17A1, 17alfa-hydroxylase and lyase; DHEA, dehydroepiandrosterone; DOC, deoxycorticosterone; HSD11B2, 11-OH-steroid dehydrogenase; SRD5A, 5alfa-reductase.

phenotype correlations that have been shown to be clinically useful. There is a good genotype/phenotype correlation in which the severity of the mildest allele determines the phenotype (14, 15, 16, 17). Homozygosity of null mutations, that is, the null genotype group, results in the most severe phenotype with salt loss in the neonatal period if untreated. An I2 splice mutation results in about 1% rest activity and is slightly less severe. The simple virilising form is most often caused by the I172N mutation. NCAH typically results from mutations having 20–70% enzyme activity, the most common one being V281L (14, 15, 17, 18) (Fig. 1). The correlation between phenotype and genotype varies in the different forms of CAH, being 100% for the null genotype form, 95% for the simple virilising form and 70% for NCAH (19).

Among the patients with NCAH, about 25–50% of those diagnosed were homozygous or compound heterozygous for two mild alleles (20, 21, 22). The

remaining patients were compound heterozygous with a more severe, classic mutation on the other allele (50–75%).

Clinical presentation

Late-onset, nonclassical CAH is usually diagnosed later on during childhood or adolescence or even in adulthood (18, 23, 24, 25). The symptoms of androgen excess may start during childhood or later in life. The spectrum of symptoms at diagnosis is related to age (Table 1). In children aged younger than 10 years, preterm adrenarche was most common (87%), while female adolescents may present with severe acne, hirsutism, androgen alopecia, clitoromegaly (11%), irregular menstruation (56%) or even primary amenorrhoea (9%) (26, 27). In adolescents and adults, typical presenting symptoms are acne, hirsutism, oligo-menorrhea or infertility.

In NCAH, the variations in phenotype depend on the severity of the enzyme deficiency and vary with age and gender. Earlier and more severe symptoms are seen in patients who are compound heterozygous for a classic mutation, that is, homozygous patients with two mild mutations have less severe symptoms compared to those who are compound heterozygous with a classical mutation (22, 28).

Males are diagnosed considerably less often than females, possibly owing to the fact that they are less prone to seek medical attention due to symptoms of androgen excess (18, 29). Hence, studies in men with NCAH are scarce. In one report on 45 males, 13 (29%) had premature pubarche before 9 years of age or hirsutism or acne (11%) (22). Gynaecomastia has been reported as the presenting symptom in two male adolescents with NCAH (30).

The symptoms at presentation are often indistinguishable from adrenarche, so that the diagnosis requires investigations. Studies in children with premature adrenarche have shown that 4–25% were diagnosed with CAH (31, 32). Genetic investigations in a cohort of 59 individuals with androgen symptoms showed that 12 had NCAH, 19 were carriers and 18 were heterozygous for a polymorphism previously discussed with regard to causing increased androgen production (32). In their cohort, the allele frequency was 77% for V281L and 7% for P453S. Among women with late-onset androgen symptoms, in adolescence or as adults, the proportion of heterozygous carriers was 1/3. Hence, carriers may have clinically significant alterations in androgen synthesis (33).

Childhood

The androgen excess in NCAH does not cause prenatal virilisation of the external genitalia in 46,XX foetuses. The increase in 17OHP in the neonatal period is usually not large enough for the children to be identified by the neonatal screening programmes, which are designed to pick up patients at risk of adrenal crisis (9, 34, 35, 36, 37, 38). Therefore, only a smaller number of individuals are identified in the neonatal period. Screening programmes with a second screen at 14 days of age are more likely to identify NCAH since the 17OHP level often increases over time in CAH (35, 36, 37, 38, 39).

The most prevalent early symptoms in patients identified during childhood are oily skin, acne or adult type body odour, pubarche or pseudopubertas praecox. Clitoromegaly and acne were each present in 20% of females younger than 10 years of age (26). Accelerated growth indicates a more pronounced androgen effect, but this cannot be seen before 1–2 years of age since androgen excess does not affect growth velocity at such an early age (40, 41). The 17OHP and adrenal androgens are converted to estrogens and may therefore cause advanced bone age. Although most children with NCAH are reported to

Table 1 Clinical presentation in individuals with non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, listed according to prevalence for males and females respectively.

Prevalence	Girls	Women	Boys	Men
↑	Premature adrenarche	Hirsutism	Premature adrenarche	Family screening
	Acne	Menstrual cycle disorders	Family screening	Acne
	Increased Growth velocity	Acne	Increased Growth velocity	Adrenal incidentaloma
	Family screening	Infertility	Acne	Infertility
	Clitoromegaly	Family screening	Gynaecomastia	
		Alopecia		
		Clitoromegaly		
		Adrenal incidentaloma		
		Short stature		

reach a final height within their target, accelerated growth and bone age advancement may, over time, lead to a compromised final height (27, 42).

Puberty and growth

Untreated patients with NCAH may enter puberty earlier than the average in the general population, in which case this affects final height and results in short stature (43, 44, 45, 46, 47). The pubertal age and peak velocity have been reported to start earlier in the group of patients with NCAH that had not been treated, by 2.3 years, on average (48). Age at diagnosis was negatively correlated with final height SDS corrected for parental height. Those who had bone age advancement at diagnosis had a significantly shorter corrected height than those who did not (49). Individuals compound heterozygous for both a mild and a severe allele had a significantly shorter final height (49). When treatment was started before bone age of 9 years, all were able to reach their target height (48). Hence, an early diagnosis and start of treatment may improve final height.

Adults

In adults, the androgen excess may have caused short stature. Increased body hair, acne, oily skin and infertility occurred in both men and women. Among women over 10 years of age, the presenting clinical features included hirsutism (59%), oligomenorrhoea (54%), acne (33%), infertility (13%), clitoromegaly (10%), alopecia (8%), primary amenorrhoea (4%) and premature pubarche (4%) (26). Hirsutism was increasingly common as the presenting symptom, but not more severe with increasing age, 50% in adolescence and 70% in middle-aged women (26). It is not uncommon that women are diagnosed while being investigated for menstrual disturbances or infertility with a PCOS-like picture (22, 26, 27, 48, 50).

Biochemistry and pathophysiology

The majority of patients with NCAH have normal ACTH levels on assessment. Cortisol production on stimulation may be normal or slightly impaired. Adrenal androgens are increased in NCAH. However, DHEAS is usually normal, while androstenedione, testosterone and dihydrotestosterone (DHT) are elevated (27, 51, 52).

The CYP21A2 deficiency results in increased 17OHP levels regardless of the ACTH increase owing to the kinetics in the enzymatic steps. The 17OHP is converted to androgen via several pathways (Fig. 2). DHT is produced from testosterone, but also via the 'back door pathway', surpassing the production of testosterone (23, 53). In addition, elevated 17OHP will, via 11-betahydroxylase activity, produce 21-deoxycortisol, which is then converted to the 11-keto forms of testosterone and DHT (11-ketotestosterone and 11-ketoDHT), which bind equally well to the androgen receptor (54). These 11-oxygenated androgens may even be better biomarkers of adrenal androgen production and treatment response than the conventional androgens (54). Reference values for the 11-ketosteroids in plasma are lacking. In order to perform a complete assessment of the androgen situation, a 24-h urinary steroid analysis should be done. The enzyme activities in the different pathways differ in the neonatal period and before and after adrenarche (55). Variations in phenotype and clinical symptoms are most likely to be due to differences in *CYP21A2* genotype, but differences in other enzyme activities involved in steroid hormone synthesis and metabolism are likely to either ameliorate or aggravate the symptoms of androgen excess in patients with NCAH.

Diagnosis

An elevated level of 17OHP is used as a marker for CAH (56). It is the biochemical hallmark of 21-hydroxylase deficiency and the main substrate for the 21-hydroxylase enzyme (Fig. 2). A concentration of 17OHP >240 nmol/L in a random blood sample is diagnostic of classic 21-hydroxylase deficiency (57, 58). In countries with neonatal screening, classic CAH is now mainly diagnosed by screening and not by symptoms alone. Neonatal screening in Sweden identifies all cases with SW CAH, but it may miss some patients with SV CAH and only 12 cases with NCAH were detected in 2.7 million screened babies (37). The majority of individuals with NCAH will not be detected by screening (35, 37, 38). Moreover, 24 of the 38 (63%) diagnosed patients with NCAH were not detected in the screening (36).

When the diagnosis of CAH is suspected later in childhood or in an adult, screening with an early morning 17OHP should be the first investigation. A value of less than 2.5 nmol/L in children and less than 6.0 nmol/L in adults has been suggested to exclude CAH (9, 31, 58, 59). It is important that the 17OHP sample is taken early in the morning and in the follicular phase in menstruating women. It has been estimated that between 2 and 11% of

patients with NCAH will be missed using this approach – at least among adults (21, 22, 60). In line with the pattern of the presenting symptoms being more severe in individuals with NCAH and one classic allele, the 17OHP level has been shown to be more elevated in individuals who were compound heterozygous for a classic and a non-classic allele, compared with those who were homozygous for non-classic mutations, regardless of age (19, 22). LC-MS/MS is more sensitive than the traditional assays for measurement of 17OHP level in the circulation. However, it is not widely available and if the cut-off levels should be changed is not clear. In order to exclude other enzyme deficiencies that can cause elevated 17OHP, such as 11-hydroxylase or P450 reductase deficiency, measurements of androstenedione, testosterone and 21-deoxycortisol should be carried out (10, 61).

The next diagnostic step if the clinical suspicion remains is the ACTH stimulation test (250 mg of cosyntropin i.v.), with a measurement of 17OHP at 60 min. This is considered to be the golden standard for the diagnosis (56). A basal 17OHP of above 15 nmol/L and/or ACTH-stimulated 17OHP of more than 30 nmol/L in males and, in females during the follicular phase, is considered to be diagnostic for NCAH (60). It has been suggested that a stimulated level of less than 30 nmol/L excludes NCAH (22). Among 140 and 160 men and women respectively with genetically confirmed NCAH, some were found to have a stimulated 17OHP of about 30 nmol/L (21, 22). Carriers may have levels overlapping those for NCAH (2). In patients with classic CAH, basal and stimulated 17OHP will typically exceed 300 nmol/L (9, 58). Stimulated levels between 30 and 300 nmol/L are often seen in NCAH. However, the stimulated level did not correlate with the NCAH genotype (22). Levels below 50 nmol/L may represent unaffected or heterozygous carriers (9). Some individuals with adrenal incidentalomas may also have levels of 17OHP above 30 nmol/L without a genetically confirmed carrier status or NCAH (62). In addition, pregnanetriol, the urinary metabolite of 17OHP, can be used in a 24-h sample to diagnose 21-hydroxylase deficiency (63), but normal values cannot completely rule out NCAH. Genetic testing should always be carried out in equivocal cases and gives useful prognostic information and guidance in treatment decisions (9, 64).

Prevalence

Classic CAH due to 21-hydroxylas deficiency is a relatively common monogenic disease with a prevalence of 1 in 15,000 live-births in most populations, according to data from 13 neonatal screening programmes including more than 6.5 million newborns (58, 65, 66, 67). The carrier frequency for a classic CAH mutation is 1 in 60 individuals.

Allele frequencies were investigated in a number of different populations and, contrary to what had been believed (68), heterozygosity for non-classic mutations was relatively common regardless of ethnicity (69). Genotyping performed among 200 Ashkenazi Jewish individuals and Caucasians showed a carrier frequency of 15% among Ashkenazi Jews and 9% among Caucasians, that is, more common among Caucasians and less so among the Jewish population than previously thought (68). The estimated disease frequency was 1/200 in US Caucasians (69). Among the African American population, both classic and NCAH are relatively uncommon (26). The prevalence among women seeking medical attention for symptoms of androgen excess was 4.2% (95% CI: 3.2–5.4%) in a meta-analysis including publications between 1980 and 2015 (27). In Russian women of Caucasian descent with androgen excess, only 1% were diagnosed with NCAH (70). The V281L mutation was by far the most common allele in NCAH (21), varying between 2 and 13.9%, with an especially high prevalence in the Ashkenazi Jewish population in New York (17, 71), followed by P30L with 0.5–2.6% and <1% for P453S. In a study from New Zealand, the carrier frequency for classic and non-classic mutations was 4 and 2% (all V281L) respectively (72), while in Spain, 7.5% carried a V281L mutation and, in Cyprus, 4.3% (18).

Treatment

In general, treatment should be reserved for symptomatic patients desiring treatment (9, 18, 27). Since, however, most patients have been identified during investigations for symptoms for which they have sought medical attention, the majority of individuals diagnosed with NCAH will receive some kind of treatment, at least for a certain period of time. It is our impression that children identified by neonatal screening seem to develop symptoms relatively early, as a sign of a more severe phenotype, and therefore often start treatment. An accelerated growth velocity and bone age may be an indication for starting treatment (Table 2), but this can only be used in children over 2–3 years of age (40).

The use of hydrocortisone is recommended in children because it has less negative effect on growth. The recommended hydrocortisone dose for classic CAH

Table 2 Indications for treatment and follow-up of individuals with non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Any symptoms of androgen excess in preschool children are indicated a hormonal imbalance and may be indication of treatment. All treatment decisions have to be individualised, in both children and adults.

Indications for treatment					Follow-up	
Preschool children	School children	Adolescence	Women*	Men*	Children	Adults
Any symptoms of androgen excess are indicating an imbalance	Oily hair, severe acne, hirsutism	Severe acne	Hirsutism, androgen alopecia, severe acne	TARTs	Every 3–12 months depending on symptoms	Annually if on treatment, otherwise every 2–3 year
Apocrine body odour alone is not an indication for treatment	Clitoromegaly	Hirsutism or androgen alopecia, clitoromegaly	Clitoromegaly	Fertility issues	Growth velocity, Weight	Weight (BMI)
Oily hair, acne, hirsutism	Premature adrenarche	A history of growth acceleration in the absence of central puberty and markedly accelerated bone age	Menstrual irregularities	Severe acne	Blood pressure	Blood pressure
Clitoromegaly	Growth acceleration in the absence of central puberty	Episodes of exaggerated fatigue during illnesses	Fertility issues	Episodes of exaggerated fatigue during illnesses	Bone age, every 1–3 years depending on symptoms	17-hydroxyprogesterone (if available: 24 h profile, using dried blood spots)
Growth acceleration, accelerated bone age	Markedly accelerated bone age	Menstrual irregularities persisting more than 2 years after menarche	Episodes of exaggerated fatigue during illnesses	Synacthen/ cosynthropin stimulated cortisol <500 nmol/L	17-hydroxyprogesterone (if available: 24 h profile, using dried blood spots)	Androstenedione
Episodes with severe exaggerated fatigue during inter-current illnesses	Episodes of exaggerated fatigue during illnesses	Primary amenorrhea	Synacthen/ cosynthropin stimulated cortisol <500 nmol/L		Androstenedione	Testosterone
Synacthen/ cosynthropin stimulated cortisol <500 nmol/L	Synacthen/ cosynthropin stimulated cortisol <500 nmol/L	Synacthen/ cosynthropin stimulated cortisol <500 nmol/L			Testosterone	Sexual hormone binding globulin
					Sexual hormone-binding globulin	Fasting glucose (or HbA1c) Bone mineral density every 3–5 years if on glucocorticoids Testicular ultrasound in males every 5 years

*Depending on patients' own decision.

is 10–15 mg/m^2 body surface and is higher in adolescence (25). The doses required for ameliorating the androgen excess are often substantially lower for patients with NCAH (25, 73). An adrenarche of clinical significance, such as acne and hirsutism, prompting the medical contact is usually treated.

As many as one-third of the diagnosed patients with NCAH have a partial cortisol insufficiency (21, 60, 74), with an ACTH-stimulated cortisol level below 400 nmol/L and 60% below 500 nmol/L. It has been suggested that a stimulated cortisol level of less than 500 nmol/L may justify daily glucocorticoid supplementation (29). Glucocorticoids can be recommended during severe illness at least for those with a suboptimal stimulation response. It important to note that when daily glucocorticoid treatment has been initiated, the hypothalamic-pituitary-adrenal (HPA) axis will be suppressed and the risk of adrenal crisis during severe stress increased. Thus, there is a need for increased glucocorticoid doses and sometimes i.v. administration during stress. It is essential that patients and their families are educated regarding treatment and stress dosing (75, 76, 77, 78, 79).

Glucocorticoids

By suppressing ACTH production, glucocorticoids can normalise the excessive androgen production, also when it cannot be explained by cortisol deficiency, but rather the changed enzyme kinetics (80). The androgen levels may even be subnormal in both males and females (81, 82). Newer preparations with extended-release hydrocortisone have been introduced lately (83, 84) and there have been experimental studies with continuous subcutaneous hydrocortisone infusion (85), better mimicking the circadian rhythm in classic CAH. However, whether or not there are any benefits regarding NCAH with these new therapies remains unclear.

Thus, the glucocorticoid preparations normally used are hydrocortisone, prednisolone and dexamethasone. Hydrocortisone is preferred during childhood due to less growth suppression than the longer-acting preparations (86). Prednisolone (1–5 mg/day divided in two doses) is often preferred in adults due to simpler dosing. Some clinicians are cautious and avoid dexamethasone altogether (4, 81, 87, 88, 89), due to concerns about a worse metabolic and bone profile. In addition, dexamethasone passes the placenta and reaches the foetus if the women become pregnant. In contrast, others prescribe dexamethasone more liberally (6), even as the preferred option in NCAH (90).

Treatment evaluation

Growth velocity, weight and bone age are normally employed to guide glucocorticoid treatment in children (Table 2), while in adults there is no consensus (91). At least annual physical examination and hormone measurements (morning 17OHP and androstenedione) are recommended by the Endocrine Society, but no guidance is given about specific targets (9). Recently, metabolites such as 11-oxygenated-C_{19} and pregnenolone sulphate have been suggested as useful biomarkers in classic CAH for disease control and long-term complications (92). However, these are not available in clinical practice and their use in NCAH has not been investigated. Dried filter paper blood samples have been shown to be reliable and convenient in the follow-up of not only classic CAH (93) but also NCAH (82). In our practice, we have dried filter paper blood samples, 24-h profiles, done at home by the patients with CAH. In our experience, a single morning 17OHP level is of limited use in glucocorticoid dose adjustment (64, 81, 82). We do our very best to keep the androstenedione and testosterone levels within the normal age-adjusted range and, in females, a ratio of testosterone to sexual hormone globulin (SHBG) of less than 0.05 (18). Since serum DHEAS levels will be suppressed below a normal age-adjusted range when normal supplementation doses of glucocorticoids are used in both women and men (81, 82), they can only be used as a marker of non-compliance.

Mineralocorticoids

Fludrocortisone medication is rarely used in NCAH but has sometimes been used possibly to minimise the glucocorticoid doses (4, 50, 81, 90, 94). Older adults with NCAH usually do not tolerate fludrocortisone due to such adverse effects as hypertension and oedema (18), especially women over 50 years of age.

Other treatment options

Other treatment options are to block the effects of androgens with antiandrogens or decrease the ovarian androgen secretion by using oral contraceptive pills or GnRH agonists (27). A 40–60% decrease in testosterone levels has been demonstrated with oral contraceptive pills, thanks to the inhibitory effect on the ovarian androgen production, together with the increased synthesis of SHBG from the liver (95). In an old randomised control study comparing the effect on isolated hirsutism in patients with NCAH, the antiandrogen, cyproterone acetate, was more

effective than hydrocortisone (96). Other antiandrogens have also been used, such as spironolactone (in spite of the anti-mineralocorticoid action), flutamide and finasteride (a 5-alpha-reductase inhibitor) (18). These drugs should not, however, be used during pregnancy. In mild cases of hirsutism, shaving, waxing, bleaching, plucking, electrolysis and laser therapy may be sufficient or be used as a complement to medical therapy (97). The use of insulin sensitisers including metformin in PCOS has been recommended against owing to their inferior effect in the treatment of hirsutism (97). However, metformin and simvastatin have been shown to produce improvements in 17OHP and androgen levels in a small number of women with NCAH, but not in PCOS, and with little or no improvement of symptoms (98, 99).

Fertility issues

Fertility is affected in both men and women with CAH (100). This is, however, related to the severity of the disease. In a national epidemiological follow-up study, women and men with NCAH were as likely to have children as controls (101). The fertility issues for men and women with NCAH will be discussed separately below.

Women

Fertility has been shown to be compromised in women with classic CAH (9, 101, 102, 103, 104). Elevated androgen and 17OHP levels result in menstrual irregularities and anovulatory cycles (9, 23). Continuous elevation of progesterone produces a contraceptive effect (100, 105). Treatment with glucocorticoids can usually improve the hormonal situation and enables conception (103, 105). The situation for women with NCAH has been much less studied, but there is a clear relationship between the severity of CAH and fertility (101). The majority of women with NCAH are able to conceive spontaneously (106, 107). Nevertheless, among women with NCAH, 10–30% have fertility complaints (22, 26). Treatment with ovulation induction is usually successful (100, 105, 108). In addition to a possible contraceptive effect caused by the hormonal imbalance, a long-standing excess of adrenal androgens may lead to endometrial atrophy, which adds to the subfertility (105). The clinical picture is PCOS-like, which may contribute to the decreased fertility (22, 26, 107, 109). Sonography showed that 25% of women with NCAH had a PCO morphology (110). It is important, however, to distinguish between PCOS and NCAH since the management differs.

Nevertheless, studies on the fertility outcome have shown that 53–68% of the women with NCAH conceived spontaneously before diagnosis and treatment (106, 107). After the start of hydrocortisone treatment, most women (78%) became pregnant without ovulation stimulation (107). Patients who became pregnant spontaneously had, overall, fewer clinical symptoms of androgen excess, although there was no difference in the frequency of mild and severe mutations between the groups (107). Glucocorticoid treatment shortened the time to conception from about 1 year to less than 6 months (111).

The pregnancies have been reported to be normal and uneventful, although this has not been described in detail for NCAH. The women may have to increase their glucocorticoid dose during pregnancy (100, 112) and regular clinical check-ups, including control of blood pressure and gestational diabetes, are recommended (100). An increased risk of miscarriage has been reported in two studies with similar rates: 26% if not treated with glucocorticoid and 6% when on treatment (106, 107). In contrast, in a retrospective study from Israel, glucocorticoid treatment did not significantly affect the frequency of miscarriage (111). Despite the conflicting results, treatment during pregnancy is often advised (27). Caesarean section is not more common in NCAH, but it has been reported (112).

The outcome of the children is excellent (64). There is an increased risk (1.4–2.5%) for a woman with NCAH to have a child with classic CAH and of having a child with NCAH, as high as 14% (106, 107). The sex of the children showed a slight preponderance of females to males, i.e., 52 to 48%, and is the opposite to what is seen in the general population with 51% males and 49% females (103, 111). The reason for this finding is not clear.

Men

Fertility in males with CAH has been reported to be severely impaired (89, 113, 114, 115, 116, 117), mainly due to hyper- or hypogonadotrophic hypogonadism. Testicular adrenal rest tumours (TARTs) were present in up to 86–94% of all adolescents and adults with CAH (114, 118). These tumours are always benign, but they may impair gonadal function by mechanical obstruction of the seminiferous tubules (119). Males with TARTs may, however, still father children (64, 114), especially if the TARTs are of limited size. Moreover, psychosexual factors may also play a role in fertility; for example,

males with CAH were less sexually active and had fewer partners throughout life (114, 120). In spite of all this, almost nothing was known about male fertility in NCAH (18) until recently (116). TARTs had only been described in occasional males with NCAH (114, 117); hence, it was assumed that the fertility would be less affected in males with NCAH. This was recently confirmed in the largest study investigating fertility outcomes including 221 males with CAH and 22 024 matched controls (116). The odds ratio (OR) for being a father among males with CAH was only 0.5 (95% CI: 0.4–0.7) and even less when adjusted for socioeconomic factors (marriage, region of residence, education and income) (OR: 0.4, 95% CI: 0.2–0.5), while males with NCAH displayed a tendency to increased fatherhood (OR: 3.7, 95% CI: 0.9–15) or at least comparable to that of controls (adjusted OR: 2.9, 95% CI: 0.4–19).

Thus, fertility does not seem to be impaired in males with NCAH, but similarly to females with NCAH, the risk of having a child with NCAH or classic CAH was significantly increased (116).

Comorbidities

Bone mineral density and fractures

In theory, since many individuals with NCAH do not start glucocorticoid treatment during childhood and are diagnosed first in young adulthood (and even then, may not start treatment) their BMD could be increased thanks to prolonged periods of hyperandrogenism. Some studies reported that adults with NCAH had a normal BMD or at least a better one than adults with a classic CAH (121, 122, 123). Similarly, in children with NCAH, the BMD was normal or at least better than that in children with classic CAH (124). However, other studies found a similar frequency of osteoporosis or decreased BMD in NCAH, compared to classic CAH (6, 123, 125, 126, 127). Fracture prevalence has sometimes been reported in CAH (82, 121, 122, 127, 128, 129) and patients with NCAH have appeared to have fewer fractures than those with classic forms (121, 122).

Obesity

Most studies on adults and children with CAH have reported an increased BMI (6, 89, 124, 125, 128, 129, 130, , 131, 132, 133, 134, 135, 136, 137, 138), but not all (4, 73, 94, 139, 140, 141, 142). The frequency of obesity did not differ between patients with NCAH and classic CAH in some studies (6, 94, 122, 124, 125, 143), while others reported a lower BMI in patients with NCAH (89). BMI has shortcomings for estimation of body fat, especially in CAH since physical activity, which is common in CAH females (144), and hyperandrogenism, may result in increased muscle mass, a higher BMI and overestimation of body fat. On the other hand, physical inactivity or hypoandrogenism owing to supraphysioloigal glucocorticoid replacement may cause decreased lean body mass and underestimation of fat mass if BMI is used (18). Since individuals with NCAH have been exposed to hyperandrogenism during an extended period, it can be assumed that they would have an increased lean mass (18). Children with NCAH have been found to have increased lean, and decreased fat mass, compared to children with classic CAH (94).

Cardiovascular disease and diabetes

There have been many studies on CAH that indicate an increased cardiometabolic risk, including insulin resistance (4, 6, 81, 89, 125, 137, 145, 146, 147, 148, 149, 150), but very few indicating an increased frequency of established cardiovascular disease (129, 151) or diabetes (including gestational diabetes) (81, 103, 151). Since most studies have been performed in children and adolescents and most of the adults in the CAH studies have been aged less than 50 years, this is to be expected because cardiovascular disease and diabetes usually develop later in life (64). In individuals with NCAH, cardiovascular diseases were more common than in controls, especially stroke, while for heart failure and venous thromboembolism, there was only a tendency for an increase (151). An occasional case of gestational diabetes has been reported in NCAH (50), but type two diabetes was four times more frequent in a study of 75 patients with NCAH, compared to 7500 controls (151). In a study on children with CAH, only those with NCAH were insulin-resistant even though they had less fat mass than those with classic CAH (94). It has been suggested that postnatal hyperandrogenism may impair insulin sensitivity, which may explain the difference (18). This is further supported by a study on newly diagnosed, untreated and non-overweight adult Chinese women with SV CAH who demonstrated impaired insulin sensitivity, compared to controls (137). Moreover, in a study on 26 adults with CAH (NCAH, n=8), only those with poor compliance had insulin resistance (125). However, another larger study on both children and adults failed to demonstrate an increased frequency of insulin resistance

in NCAH, compared to classic CAH (6). Androgen excess in females and low testosterone levels in males can impair insulin sensitivity (152, 153). Thus, supraphysiological glucocorticoid treatment, which is often assumed to be the cause of insulin resistance, may not be the only reason for impaired insulin sensitivity in CAH. No glucocorticoid or too low glucocorticoid doses may also result in insulin resistance via androgen excess (18).

Psychiatric diseases

Psychiatric disorders in CAH have only been reported in a few studies, and then mostly in classic CAH (129, 154, 155, 156). These studies have generally shown an increased frequency of psychiatric diseases (129, 154, 155), depression (156), alcohol misuse (154, 155) and suicidality (129, 154). Only phobic anxiety disorders were increased in women with NCAH (155), and psychotic disorders in males with NCAH compared to controls (154); the number of individuals with NCAH was, however, limited, which makes interpretations difficult.

Voice pathology in females

Prolonged hyperandrogenism may affect the laryngeal tissue mass, leading to a lower fundamental voice frequency (157). More voice issues, including a deeper voice compared to controls, have been identified in women with CAH (158). These issues were associated with a late CAH diagnosis and poor compliance, but a few women with CAH had a normal voice in spite of poor compliance and a late diagnosis (158). Hyperandrogenism had given 7% of the women with CAH voice problems; however, 45% of the patients themselves claimed to have a low-pitched voice (170). Among the women with NCAH, 50% had, subjectively, a 'dark' (i.e. low-pitched) voice (159).

Mortality

Very little is known about the mortality in NCAH. With the advance of medicine (introduction of glucocorticoid replacement and neonatal screening in addition to increased awareness) more individuals with classic CAH survive (36). Generally speaking, patients with CAH had an increased mortality rate (hazard ratio 3–5) and died 6.5–18 years earlier, compared to controls (77, 156). Mortality was not significantly increased, however, in the NCAH group, possibly due to power issues. Among those with NCAH, two-thirds died of a cardiovascular condition and one-third of an adrenal crisis, but all with a cardiovascular condition had a concurrent infection noted on the death certificate (77). Thus, all deaths in NCAH patients may have been related to an adrenal crisis, thereby highlighting the importance of stress dosing in patients with NCAH on glucocorticoid therapy.

Adrenal tumours

Chronically elevated ACTH levels can result in adrenal cortex hyperplasia with subsequent tumour formation (62, 160, 161). In patients with known classic CAH 11–58% will have at least one adrenal nodule detected if a CT or a magnetic resonance tomography has been performed (162, 163), and an even higher prevalence was found in an older cohort (82%) (160). The prevalence in NCAH is, however, unknown. On the other hand, adrenal incidentalomas, that is, adrenal lesions found serendipitously by imagining performed for other reasons than suspected or known adrenal disorder or malignancy (164), have sometimes been the initial presentation of NCAH, both in case reports and adrenal incidentaloma cohorts (62, 78, 165, 166, 167, 168). In a recent meta-analysis, 0.8% (only genetically confirmed cases) and 5.9% (all cases) of adrenal incidentalomas were associated with CAH and 81% of all cases were associated with NCAH (169). Moreover, there was a positive linear relationship between the 17OHP level and the tumour size in these patients with untreated CAH (169). In spite of adrenocortical cancer being extremely rare in CAH (18, 169), when an adrenal tumour is discovered a conventional evaluation needs to be performed to exclude other tumours that may require adrenalectomy (18).

Quality of life

Studies on the quality of life (QoL) in NCAH are scarce. In a national epidemiological study including 75 individuals with NCAH (56 females), the patients had worked during longer periods and had fewer sick leaves, but the women had disability pensions and social welfare benefits more often than the 7500 controls (101). Other than in this study, all or the majority of patients with CAH included in QoL studies have had the classical phenotype. The reports are inconsistent and indicate varying degrees of impaired

QoL (18, 170, 171, 172, 173, 174). The outcome of genital surgery and satisfaction with sexual function affect the general wellbeing and are likely to affect the QoL of women with classic CAH, especially women with the null and I2 splice genotypes (175, 176). Individuals with NCAH have often had long periods of exposure to elevated androgen levels before diagnosis but generally have not had genital surgery; hence, their QoL can be expected to differ from that in classic CAH. In a study comparing QoL in CAH with primary adrenal insufficiency, patients with CAH were reported to have a better QoL (177), possibly because they have never experienced a time without their disorder, in contrast to patients with an acquired disorder (64). The type of glucocorticoid used for treatment has been reported to affect QoL, with prednisolone or dexamethasone resulting in a worse QoL in one study, but there have been conflicting results (120, 178). To our knowledge, there are no studies comparing QoL in individuals with NCAH with or without treatment.

Follow-up and transition into adult care

The transition period, into adult care, is an especially difficult time for patients with a less severe disease, who may not fully encompass the long-term effects of their condition. Information and patient education is the basis for all health care decisions and is even more important in adolescents and young adults. We propose that all individuals with NCAH are followed up regularly (Table 2), even those with no or minimal symptoms such as males due to the potential long-term consequences of NCAH. Appropriate transition into adult care needs should be ascertained (171).

Conclusion

NCAH is a relatively common disorder regardless of ethnicity, but most cases are never diagnosed, especially in males. A baseline measurement of 17OHP may be used for screening, but the ACTH stimulation test with a measurement of 17OHP is the gold standard. We advocate a *CYP21A2* mutation analysis to verify the diagnosis, for genetic counselling and for better prognostic and treatment guidance. Most patients are diagnosed in adolescence and adult life with hirsutism, acne, a PCOS-like picture and fertility issues. Many men with NCAH may never seek medical attention and therefore escape diagnosis. Although treatment is somewhat controversial, an early diagnosis and start of treatment may have positive implications on growth and be relevant for preventing and ameliorating the symptoms and consequences of androgen excess that develop over time. Glucocorticoids will improve symptoms of androgen excess and fertility, but they may result in long-term complications, such as obesity, insulin resistance, hypertension, osteoporosis and fractures. It is important to know that treatment will lead to a secondary cortisol insufficiency. Regular clinical monitoring to avoid risk factors and improve the clinical outcome is recommended. Studies focusing on the specific difficulties patients with NCAH face, both those with a late clinical diagnosis and those with a neonatal diagnosis obtained by screening, are warranted.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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