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REVIEW

Clinical outcomes in the management of congenital adrenal hyperplasia

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Abstract Congenital adrenal hyperplasia (CAH) is a group of disorders affecting adrenal steroid synthesis. The most common form, 21-hydroxylase deficiency, leads to decreased production of cortisol and aldosterone with increased androgen secretion. In classic CAH glucocorticoid treatment can be life-saving, and provides symptom control, but must be given in an unphysiological manner with the risk of negative long-term outcomes. A late diagnosis or a severe phenotype or genotype has also a negative impact. These factors can result in impaired quality of life (QoL), increased cardiometabolic risk, short stature, osteoporosis and fractures, benign tumors, decreased fertility, and vocal problems. The prognosis has improved during the last decades, thanks to better clinical management and nowadays the most affected patients seem to have a good QoL. Very few patients above the age of 60 years have, however, been studied. Classifying patients according to genotype may give additional useful clinical information. The introduction of neonatal CAH screening may enhance long-term results. Monitoring of different risk factors and negative consequences should be done regularly in an attempt to improve clinical outcomes further.

Keywords 21-Hydroxylase deficiency · Height · Tumor · Cardiovascular risk · Fertility · Insulin resistance

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Introduction

In 1865, an astonishing case was described by the Italian Professor of anatomy Dr. Luigi De Crecchio [1]. He had conducted an autopsy on a certain Giuseppe Marzo who had a 6-cm long penis with first-grade hypospadia. No testes were found, but normal vagina, uterus, tubes, and ovaries. The adrenal glands were greatly enlarged. Giuseppe had been considered a female at birth but had been declared male at 4 years of age. Everybody close to him described him as a typical male socially and sexually. He experienced many episodes of vomiting and diarrhea and died in his 40s after such an episode. This case report is generally considered the first description of congenital adrenal hyperplasia (CAH) and several case reports followed. In 1939, electrolyte disturbances similar to those in adrenal insufficiency but with excessive androgen excretion were reported in a CAH boy. He responded well to treatment with sodium chloride and adrenocortical extract [2]. In the early 1950s, Wilkins [3, 4] introduced glucocorticoids in the treatment of CAH, and was also the first to describe that cortisone suppressed the elevated adrenal androgens. In 1984, White et al. [5] reported that CAH results from mutations in the *CYP21* gene encoding the steroid 21-hydroxylase.

Most patients with this disorder need life-long treatment and medical surveillance. The management throughout childhood and adolescence is extremely important for the quality of life (QoL) in adulthood. The detailed handling in the pediatric patient or the genital surgery in females will, however, not be discussed in detail; the present review, which will mainly focus on the situation during adult life and clinical outcomes of bone health, cardiometabolic systems, tumors, fertility, pregnancies and offspring, and voice characteristics. The review is based on articles addressing

these topics found in PubMed and published in English until 2011 using the search terms "congenital adrenal hyperplasia" and "21-hydroxylase deficiency". Older references are selected from articles retrieved by the initial search.

Physiology

CAH is an autosomal recessive disorder affecting the adrenal steroid synthesis and is the most common cause of genital ambiguity in 46XX infants [6, 7]. More than 95% of all CAH cases are due to reduced 21-hydroxylase function leading to variable degrees of cortisol and aldosterone deficiency in addition to androgen excess [6, 7]. The reduced cortisol production stimulates ACTH secretion from the pituitary gland via negative feed-back and the elevated ACTH levels promote adrenocortical growth causing adrenal hyperplasia. Steroid precursors accumulate directly proximal to the 21-hydroxylase block, and are shunted into the androgen pathway (Fig. 1). An adequate cortisol concentration is a necessity for adrenomedullary organogenesis and epinephrine production. Hence, epinephrine production is decreased in classic CAH [7]. In this article, CAH refers to 21-hydroxylase deficiency if not stated otherwise.

Clinical presentation

CAH is clinically classified into three phenotypes: the two classic forms salt-wasting (SW) and simple virilizing (SV) CAH, and the non-classic (NC) CAH. Female infants with classic CAH demonstrate virilized external genitals at birth while male infants have no overt signs of CAH except variable and subtle hyperpigmentation and penile enlargement. Both females and males with the SW form have severe aldosterone deficiency from birth resulting in salt loss. If not recognized and adequately treated during the first week of life, the infants will not survive. Males with the SV form usually present with early virilization at age 2–4 years [7]. In our Swedish cohort of adult patients, born before the introduction of neonatal screening, all the SW patients were diagnosed during the first week; SV females were usually diagnosed during infancy, whereas the SV males were detected at 3–28 years of age [8, 9].

The virilization of external genitals may need surgical correction. There are no controlled studies of either the best age or the optimal methods for feminizing surgery. In recent guidelines, it is suggested that in severe cases (Prader stage $\geq$3), clitoral and vaginal surgery can be considered in infancy [10]. In other cases, it is debated whether surgery should be carried out early in life or be postponed until adolescence when the patient can participate in the decision-making process [11]. In our cohort of adult CAH women, the most preferred early timing of surgery, but many also favored surgery at puberty when proper information could be given [12].

In severe neonatal virilization even incorrect sex assignment can occur [6]. One example is a patient of ours shown in Fig. 2. In cultures valuing boys more than girls and/or in developing countries where the diagnosis is delayed these females are more likely to be brought up as males [13, 14].

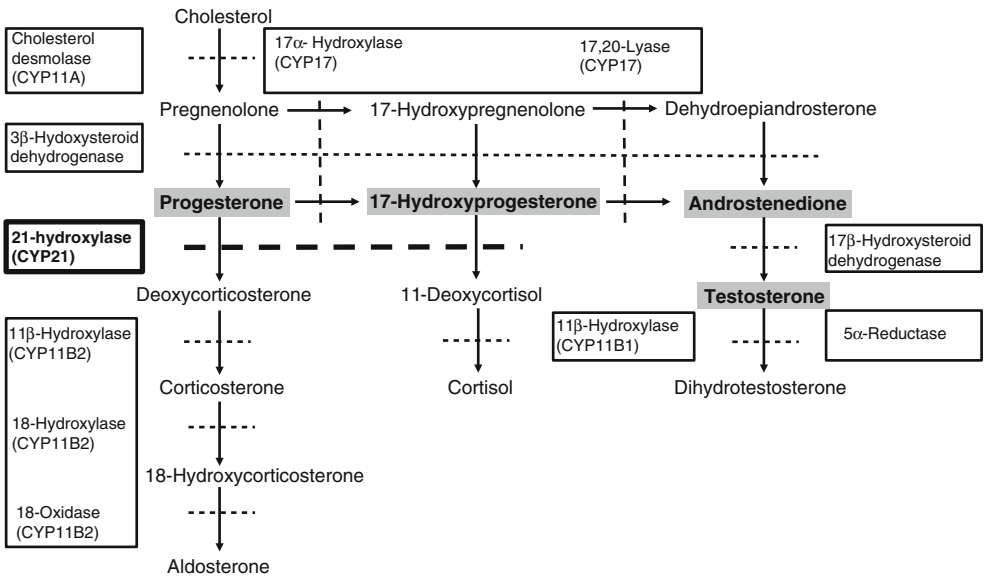

Fig. 1 Steroid synthesis in the adrenal cortex. The pathways of aldosterone, cortisol, and androgen synthesis and the six enzymatic steps from the precursor cholesterol are shown. In CAH, 21-hydroxylase is the enzyme most often affected and the corticosteroids increased in this condition are *highlighted*. Within the *brackets* are the genes coding for the various shown enzymes

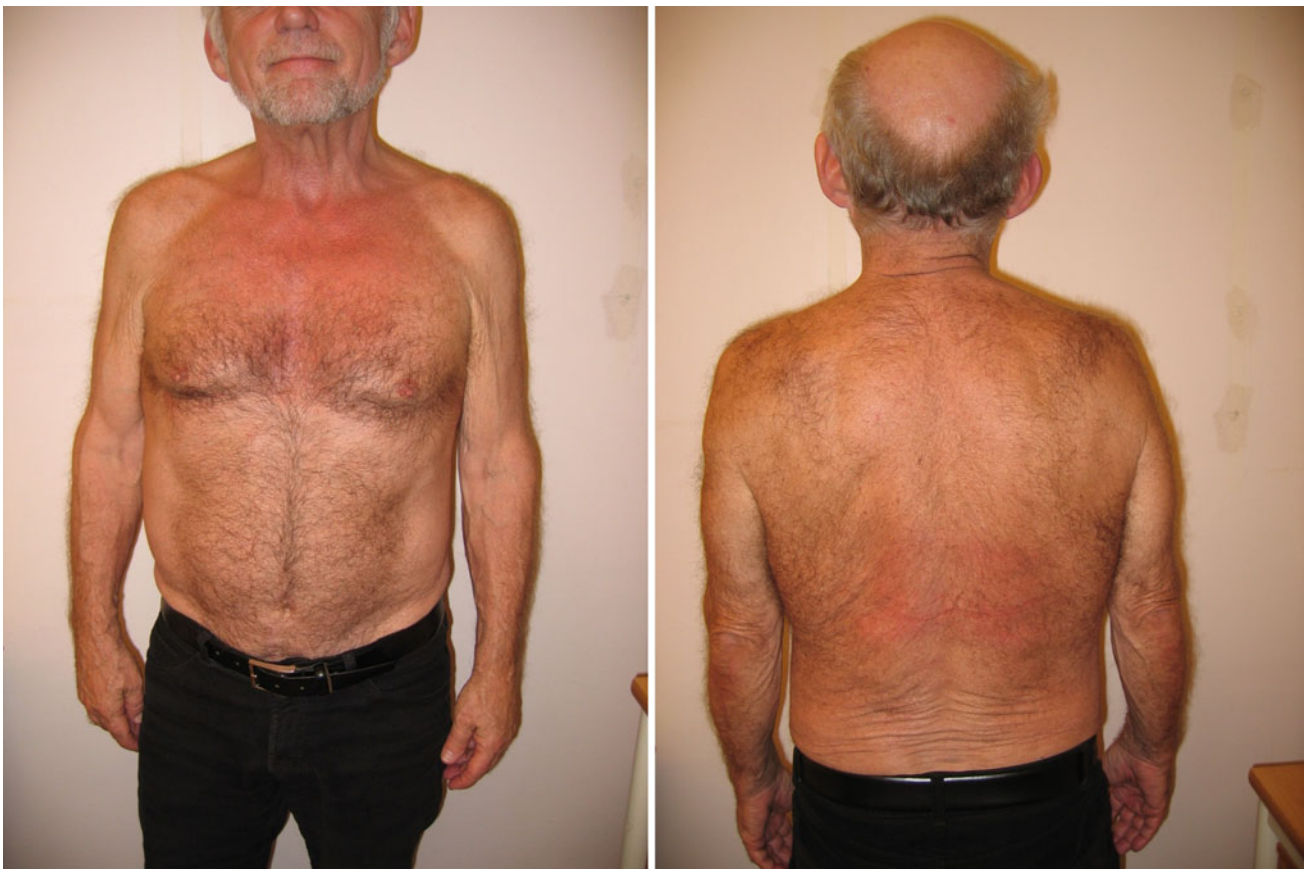

Fig. 2 A 61-year-old CAH patient (SV, I2 splice) with karyotype 46XX, treated with testosterone since puberty

NC CAH individuals have no ambiguous genitalia at birth, but can present at any time postnatally with signs of androgen excess. In a multicenter cohort study of 220 NC women by Moran et al., 11% were diagnosed before 10 years of age and 80% between 10 and 40 years of age. In the younger group, 92% had presented with premature pubarche, while the older ones had been investigated for hirsutism (59%), oligomenorrhea (54%), acne (33%), infertility (13%), alopecia (8%), primary amenorrhea (4%), and premature pubarche (4%) [15]. The clinical presentation in the polycystic ovary syndrome (PCOS) and NC CAH can be indistinguishable [16], and the latter has to be excluded before diagnosing PCOS [17]. In males, little has been reported on NC CAH, the majority being diagnosed during family screening [18]. An over-representation of both undiagnosed patients with NC CAH and female carriers (i.e., patients with only one *CYP21A2* allele mutated) has been reported from clinics treating severe acne [19–21]. Some males and females with NC CAH have very discrete symptoms, and are not diagnosed until old age if ever [22].

Neonatal screening

To avoid neonatal death from undiagnosed salt-wasting and prevent erroneous sex assignment, many countries in the industrialized world have introduced neonatal screening for CAH using measurements of 17-hydroxyprogesterone (17OHP) [23]. Since the introduction of neonatal screening of all newborns in Sweden 1986, no neonatal death from salt-wasting has been recorded, while in the years 1969–1986 at least two boys had died of salt-wasting in the neonatal period and several children had been critically ill [24]. In UK, where neonatal screening still awaits introduction, the number of newborn girls diagnosed with the most severe CAH is four times higher than that of boys [25]. With the knowledge that the incidence is similar in the two sexes, these data indicates that many boys may have died before being clinically diagnosed. This is in accordance with the fact that one quarter of the CAH girls and three quarters of the CAH boys in the Swedish screening program were diagnosed only by screening and would not have been detected by clinical investigation alone [24].

Prevalence

Data from 13 neonatal screening programs with more than 6.5 million newborns included, demonstrated that 21-hydroxylase deficiency is quite common with a frequency of the classic form of one in 15,000 live-births [7]. Thus, the carrier incidence is roughly one in 60 individuals. However, the incidence of classic 21-hydroxylase deficiency varies widely, depending on ethnicity and geographical location being highest in two very isolated areas with relatively small populations: the Yupic Eskimos in Alaska (one in 282), and on the island of La Réunion in the Indian Ocean (one in 2,141), but even the inhabitants of the big city of Rome in Italy have a high frequency (one in 5,580 Caucasians) [26]. In contrast, classic 21-hydroxylase deficiency is rare in Afro-Americans (one in 42,309) [27].

NC CAH is more common than classic CAH and is usually not detected by screening. In the heterogeneous population of New York City, 1 in 111 (0.9%) was affected, but the prevalence varied between the different ethnicities, being highest in Ashkenazi Jews (3.7%) [28]. NC CAH has been claimed to be the most frequent autosomal recessive disorder in man [29].

Molecular genetics

The molecular genetics of 21-hydroxylase have been well characterized [30]. The gene encoding 21-hydroxylase is named *CYP21A2*. Approximately 95% of all mutations causing 21-hydroxylase deficiency are deletions/large gene conversions of the entire *CYP21A2* and/or a few point mutations [6, 31]. A good genotype–phenotype correlation has been shown in 21-hydroxylase deficiency [31, 32], although some exceptions may occur.

The milder mutation of the two affected alleles determines the phenotype. Although three different phenotypes exist, four genotype groups can be identified with the mildest allele representing the group: null, I2 splice, I172N, and NC. Null refers to mutations completely abolishing 21-hydroxylase activity and is associated with the SW phenotype. I2 splice retains a very low but measurable level of activity and is usually associated with SW but in a few cases SV. I172N is less severe and most often found in SV, but is rarely associated with SW. The NC genotype group includes mutations such as V281L and P30L with enzyme activities of between 30 and 50% and is as a rule associated with NC phenotype (Fig. 3) [6, 31].

The Endocrine Society Clinical Practice Guidelines from 2010 recommends genotyping for purposes of genetic counseling and for confirmation of the diagnosis especially in NCCAH when the ACTH-stimulation test is equivocal [10]. In our experience, another advantage of mutation analysis is that the clinical course can be predicted and serious consequences can be prevented. This applies for instance to females with the null genotype who are more severely affected with respect to fertility, social functioning and psychosexual issues than other genotype groups and may need extra support [33–35].

Mutation	Clinical severity	Phenotype	Enzyme activity (in vitro) Percentage of normal
Null		SW	<1%
I2 splice		SW/SV	
I172N		SV	2-10%
P30L		SV/NC	
V281L and P453S		NC	30-50%

Fig. 3 The most common mutations in *CYP21A2*, their phenotype and 21-hydroxylase activity in vitro. The null genotype group contains the following mutations: Deletion, Del 8 bp E3, Cluster E6, L307insT, Q318X, and R356W

Corticosteroid treatment

Glucocorticoids

Individuals with SW CAH did not survive the neonatal period before the launch of glucocorticoids in the beginning of the 1950s. Glucocorticoids substitute for the cortisol insufficiency as well as decreasing ACTH production and secretion resulting in lower adrenal androgens, i.e., provide for the possibility of survival and symptom control. During the last decades, fear of long-term side effects of supraphysiological glucocorticoid supplementation has come into focus [6, 7, 10]. The lowest possible dose that normalizes increased adrenal androgens and supplements the cortisol insufficiency is recommended today. Unfortunately, existing formulations of glucocorticoids cannot imitate the physiological circadian rhythm of cortisol secretion leading to over-treatment and suppression of androgens in many cases [36]. Alterations in cortisol pharmacokinetics during puberty can further complicate glucocorticoid treatment [37]. However, continuous subcutaneous hydrocortisone infusion has recently been introduced on two CAH adolescents with good result [38, 39], this may be an option in the future for cases where acceptable control cannot be achieved with conventional formulations.

Whereas growth velocity and bone age remain the gold standard for guidance of corticosteroid treatment in children, there is no consensus on which laboratory and clinical parameters should be used to monitor therapy in adults

[40]. The recent Endocrine Society Guidelines state that at least annual physical examination and appropriate hormone measurements should be performed but optimal levels for the commonly used 17OHP and androstenedione have not been defined [10]. Our experience is that morning levels of 17OHP have a wide range, and are difficult to interpret [8]. Instead, our preference is for diurnal 17OHP curve with dried blood spots, done at home by the patients.

Hydrocortisone (10–15 mg/m^2/day divided in three doses) is the glucocorticoid of choice during childhood as it affects growth less than other longer acting preparations [41]. Intermediate-acting glucocorticoids, such as prednisolone (5.0–7.5 mg/day divided in two doses) and long-acting glucocorticoids, such as dexamethasone (0.25–0.50 mg at bedtime or divided in two doses), may be an option at or near the completion of linear growth [7, 10]. Prednisolone is usually the preferred glucocorticoid in adults [8, 9, 42–44]. Prednisolone and dexamethasone have minimal mineralocorticoid effect in the doses given contrary to hydrocortisone. Cortisone acetate is not recommended because it has to be converted to cortisol for biological activity and this conversion can be impaired due to low 11β-hydroxysteroid dehydrogenase activity [45].

Mineralocorticoids

Fludrocortisone is used for mineralocorticoid replacement and is generally mandatory in SW, but also recommended in SV as it reduces vasopressin and ACTH levels and minimize the glucocorticoid doses required [7, 41]. Some degree of aldosterone insufficiency can be found in all individuals with 21-hydroxylase deficiency, even in those with NCCAH [46]. Thus, fludrocortisone has sometimes been used even in NC [8, 9, 16, 43, 47]. The aim should be to keep plasma renin or plasma renin activity in the range from mid-normal to slightly elevated which is usually achieved with doses around 0.1 mg in adults. Older adults normally benefit from lower doses (0.05–0.025 mg) due to side-effects (hypertension and edema). The doses are higher in children than in adults [10], and the phenotype can change with recovery of salt loss due to increased production of mineralocorticoids over time [48]. The dose of fludrocortisone is independent of body size and in infancy addition of salt tablets is usually necessary [6].

Potential health problems and QoL in adults with CAH

There are a number of threats to adult health in classic CAH patients. The life-long supraphysiological glucocorticoid therapy can negatively affect bone health and has also the potential to increase the cardiovascular risk. Under-treatment may result in continuous ACTH stimulation facilitating the formation of adrenal tumors. Fertility is affected by testicular adrenal rest tumors (TARTs) in males and by external genital malformation and its treatment in females. Elevated prenatal androgens affect sexual and social orientation in women. These issues are reviewed below.

Reports on self-perceived QoL are not entirely consistent. In five studies where in total 447 adult CAH patients with 21-hydroxylase deficiency, 321 women and 126 men were investigated, varying degree of impairment in QoL were found [33, 42, 43, 49, 50]. No difference from controls was found in two reports of 8 and 44 CAH women, respectively [51, 52]. Even significantly better QoL compared to controls was seen in 33 patients from Finland [53]. CAH patients had better QoL compared to patients with primary adrenal insufficiency [50]. The probable reason is that patients with congenital disorders have never experienced anything else while patients with acquired disorders compared with previous health. However, the overall QoL in adult women with CAH is affected by the both type of mutation and genital operative procedure [12]. One aspect of QoL, sexual satisfaction, was similar in CAH women and controls, but when examining the different genotypes the most severe one, the null group had less satisfaction compared to the other genotypes [34]. Some features of QoL, in particular some physical concerns, may in fact be more of a concern for the clinician than for the CAH patient [52].

Clinical outcomes of bone health

Final height

Most CAH patients do not reach their predicted final height. A recent systematic review and metaanalysis of 35 studies found that final height was −1.38 SDS. Corrected final height was −1.03 (final height SDS − midparental height SDS) [54]. In our Swedish cohort of 93 CAH patients, males were more negatively affected than females, with −1.85 versus −1.3 SDS from the population norm. Only 10% of patients were shorter than −3.0 SDS. In classic CAH, there was a trend to a better height outcome in younger (<30 years) than in older patients [8, 9, 55]. This positive trend agrees with the findings in the metaanalysis suggesting improved outcome during the years most likely due to optimized management [54]. Various factors may have an impact on height development in CAH. Early diagnosis and treatment improved final height in some [56–58], but not in all the studies [59–61]. Final height improved with good compliance [56]. Positive effects of mineralocorticoid supplementation to optimize final height have also been reported [57]. Pooled data in the metaanalysis also showed a higher final height in those

taking mineralocorticoids than those who did not. Moreover, no correlations were found between height and age at diagnosis, gender, type and dose of steroid, and age at onset of puberty [54]. The authors acknowledged, however, that the quality of evidence was very low because of methodological differences and certain limitations in included studies.

Bone mineral density (BMD) and fractures

As mentioned above, the unphysiological glucocorticoid doses can be harmful for the maintenance of bone mass via multiple mechanisms [62], leading to fragile osteoporotic bone that is more prone to fractures, the most severe consequence. Osteoporosis is a treatable condition and fracture risk can be estimated by measurements of BMD by dual-energy X-ray absorptiometry (DXA).

The majority of studies have demonstrated decreased BMD values in adult CAH [43, 63–68] and a few have shown normal BMD [69–72] (Table 1).We found, e.g., 73% of CAH women older than 30 years of age to be osteoporotic/osteopenic compared to 21% of controls [63]. BMD was equally negatively affected in the three most common classic genotypes, whereas females with NC CAH had normal BMD compared to controls. Fracture prevalence has only been reported from this study. The frequency was elevated in that 30% of patients versus 3% of controls had experienced at least one fracture. If only osteoporotic fractures were accounted for, the difference between CAH females and controls was almost significant [63]. Unfortunately, the trauma that led to fractures was not ascertained thus it cannot be ruled out that difference in lifestyle between CAH women and controls partly influenced the results, as the patients had more typically male-dominated occupations and interests [33].

In children and young adults, BMD data have been even more diverse with BMD increased [73], normal [74–76], or decreased [77]. Some studies of children found normal BMD if the entire cohort was evaluated but decreased BMD in subgroups such as boys [78], at puberty [79], or in long-term-treated girls [80].

The overall discrepancies may reflect differences in age of patients, type and severity of enzyme deficiencies, and various therapeutic regimes as well as diagnostic difficulties in growing individuals. Negative correlations between long-term glucocorticoid dose and BMD have been reported [66, 67, 81], and dexamethasone may be the most harmful glucocorticoid for BMD [66]. Thus, not only glucocorticoid treatment but also supplementation, that has to be given in an unphysiological manner and often in slightly supraphysiological doses, can lead to osteoporosis. Increased risk of hip fracture in Addison's disease has also recently been reported [82].

Table 1 Studies of BMD measured by DXA in adult CAH patients with 21-hydroxylase deficiency

Study	CAH patients M/F, n	Age (years)	Controls	BMD in CAH versus controls	Correlation BMD and GC dose	Comments
Jaaskelainen and Voutilainen [66]	16/16	16–52	National reference data	Decreased	Neg cumulative	
Guo et al. [69]	3/6	19–65	Healthy, age-, sex- and weight-matched, $n = 11$	Similar	ND	Bone turnover decreased in CAH
Mora et al. [70]	11/19	17 ± 2	Healthy, similar age, $n = 73$ (35 F)	Similar	None	BMD adjusted for BMI
Hagenfeldt et al. [67]	0/13	20–29	Healthy, age- and sex-matched, n = 12	Decreased	Neg cumulative	
Stikkelbroeck et al. [71]	15/15	17–25	Healthy, age- and sex-matched, $n = 30$	Similar	None	
Christiansen et al. [72]	10/8	18–33	Healthy, age 20–38, $n = 120$ (80 F)	Decreased	None	Similar vs controls if height adjusted
King et al. [65]	0/26	21–71	Unaffected sisters, $n = 9$	Decreased	ND	BMI pos correlated to BMD
Sciannamblo et al. [68]	15/15	16–30	Healthy, age 16–30, $n = 138$ (84 F)	Decreased	None	Also decreased if height adjusted
Falhammar et al. [63]	0/61	18–63	Age- and sex-matched, $n = 61$	Decreased	None	Also decreased if height adjusted. Fractures increased. Pos correlation BMD and lean and fat mass
Bachelot et al. [64]	9/36	18–47	As provided by the DXA machine	Decreased	None	Pos correlation BMD and BMI
Arlt et al. [43]	77 (total)	Unclear	As provided by the DXA machine	Decreased	ND	

M male, *F* female, *GC* glucocorticoid, *ND* not done, *Neg* negative, *Pos* positive, *BMI* body mass index

Clinical outcomes of the cardiometabolic systems

The glucocorticoid doses used in CAH individuals are potentially harmful and may bring an increased risk of obesity, type 2 diabetes, dyslipidemia, hypertension, and cardiovascular morbidity and mortality. So far, neither increased cardiovascular morbidity and mortality nor increased prevalence of type 2 diabetes has been found in CAH patients [8, 9]. This is expected since very few studied patients have been older than 50 years of age. An increased frequency of gestational diabetes, a strong predictor of future type 2 diabetes, has, however, been reported [8, 35]. Until we have larger studies with higher number of older CAH individuals we have to examine relevant risk factors to predict the future cardiometabolic morbidity and mortality.

Evaluation of fat and lean mass

Obesity, particularly visceral obesity, is a well-known risk factor for type 2 diabetes and cardiovascular morbidity and mortality. Most studies have found an increased body mass index (BMI) in adults and children with CAH [43, 64, 65, 67, 71, 79, 83–87], but not all [9, 47, 76, 78]. BMI can, however, be unreliable as an estimate of body fat in CAH. In the women, increased muscle mass due to androgen excess from under-treatment or from intense physical activity, often practiced in CAH women [33], can overestimate body fat if BMI is used. In contrast, in patients who are physically very inactive or severely over-treated with glucocorticoids, lean mass may be low and BMI may under-estimate fat mass.

Waist circumference and the waist-to-hip ratio are considered better predictors of adverse outcomes than BMI [88], but the experience of body circumferences in CAH individuals is limited. We found that waist circumference and waist-to-hip ratio were similar to age-matched controls in CAH individuals <30 years, but higher than in both controls and younger counterparts in older CAH women and men [8, 9].

DXA offers a precise, more reliable and straightforward way of assessing total and regional fat and lean mass than the anthropometric measurements. Four studies in children and young adults with CAH each including 13–30 subjects have all demonstrated increase in fat mass [67, 71, 72, 78]. In contrast, we found that fat mass in younger adult males and females was similar to age-matched controls but increased in males >30 years [8, 9]. Our women with CAH ≥30 years of age demonstrated instead increased lean mass in spite of their currently suppressed androgens [8], which could reflect previous under-treatment and/or a different life-style. Interestingly, two of the previous studies only found increased fat mass in male but not in female CAH patients [72, 78]. Our older CAH males had also lower testosterone levels than controls [9], if this is a cause or a consequence of increased fat mass remains unclear.

Insulin resistance

As mentioned previously the prevalence of type 2 diabetes is not increased in CAH patients but a high rate of gestational diabetes has been found [8, 35]. Insulin resistance, another risk factor for type 2 diabetes, has been evaluated by use of various methods in CAH patients usually with the homeostasis model assessment (HOMA) [43, 47, 64, 86, 87, 89–95], or with oral glucose tolerance test [9, 47, 64, 87, 91, 95]. IV glucose tolerance test [96], HbA1c [9], or forearm model combined with local indirect calorimetry [97] have also been used. Not all have had controls, thus the frequency of impaired insulin sensitivity is problematic to evaluate [43, 64]. Most reports to date have demonstrated increased insulin resistance [9, 47, 86, 91–93, 95–97]. We have found impaired insulin sensitivity only in patients ≥30 years of age [8, 9, 89]. Even if only non-obese CAH women aged ≥30 year old were compared with non-obese controls, CAH women still had increased insulin resistance [89]. In contrast, male adult non-obese CAH cases had similar insulin sensitivity as non-obese controls [9]. One trial reported improved insulin sensitivity in CAH patients with pioglitazone treatment [98].

Interestingly, in one study, only NC children and not classic CAH children were insulin resistant presumably due to adverse metabolic effects of prolonged postnatal androgen excess in NC [47]. Moreover, 30 newly diagnosed and untreated female Chinese young adult cases of SV CAH had reduced insulin sensitivity compared to controls [87]. One study with only NC CAH females found similar insulin sensitivity compared to controls but the diagnosis was not confirmed genetically and none of these patients used glucocorticoids [94]. It is often assumed that supraphysiological glucocorticoid supplementation is the reason for increased insulin resistance in CAH individuals. However, elevated androgens in females and decreased testosterone in males may lead to insulin resistance [99, 100], thus too low glucocorticoid dose may also increase insulin resistance.

Lipids

Lipid profiles in CAH children and adults on glucocorticoid therapy have most often been reported as being similar to controls [8, 9, 47, 91]. We even found more favorable HDL/LDL ratio in a subgroup of women ≥30 years compared to controls [8]. In addition, higher HDL in CAH adults compared to BMI-matched controls has recently been demonstrated [90]. No difference in LDL existed

between over-weight and lean adult CAH patients [64]. In contrast, Arlt et al. [43] reported in a large cohort that many adults with CAH had dyslipidemia. Lack of controls, however, made interpretation difficult. Higher triglycerides in children [101] and lower HDL in children and adults [95] compared to controls have been reported by others. Untreated SV CAH women had higher triglycerides and lower HDL compared to controls, probably due to hyperandrogenism [87].

Other cardiometabolic risk markers

We have reported elevated liver function tests in particular gamma-glutamyltranspeptidase (GGT) in CAH adults [9, 89]. The levels were typically within the normal range but higher than in controls. This finding may suggest non-alcoholic fatty liver disease (NAFLD) but confirmatory investigations has not been carried out. NAFLD results in an increased morbidity and mortality with type 2 diabetes and cirrhosis being risk factors for death [102]. Moreover, GGT has been shown to be independently correlated with cardiovascular mortality even in the normal range [103]. NAFLD has been reported in endogenous Cushing's syndrome [104], long-term glucocorticoid therapy [105], and in PCOS [106].

Several other risk markers measured in serum have been associated with cardiovascular and metabolic disease. Some of them have occasionally been investigated in CAH individuals but rarely pointed to increased cardiovascular risk. No increase in comparison to control populations were found when measuring Lp(a) (adult CAH males)[9], CRP (untreated SV CAH females)[87], homocysteine(NC CAH women) [94], and IL-6, IL-18, PAI-I, uPA, tPA, tPA–PAI-1 complex (adults) [90]. Homocysteine levels even indicated decreased risk in CAH males [9] as did decreased CRP in CAH adults [90] and elevated adiponectin levels in children, adolescents, and adults with CAH [90, 107]. In contrast, low adiponectin in untreated adult SV CAH females indicating increased risk [87].

In CAH adults, leptin levels were similar to BMI-matched controls [90]. In children and adolescents elevated levels were reported from two studies [92, 108], one found that elevations were dependent only on known risk factors (BMI, sex, and age) [85], and one found leptin to be equal, but soluble leptinreceptor concentrations lower than in BMI-matched controls which is compatible with a higher risk to develop obesity [86].

Blood pressure

Blood pressure has not shown to be severely affected in 21-hydroxylase deficiency although studies have shown partly divergent results [8, 9, 43, 47, 87, 90, 91, 109–114]. In children with classic CAH, blood pressure was normal during the first year of life [114]. In children and adolescents, 6.6% were reported to have hypertension in a retrospective chart review [112], and ambulatory 24 h blood pressure measurements were overall elevated [109, 113]. Modest blood pressure elevation within the normal range during daytime [110] and during hospital admission has been reported [111]. Blood pressure levels correlated to the degree of obesity in some studies [109, 113] whereas obesity was unable to predict hypertension in another study [112].

In NC CAH children and adolescents, a single measurement of blood pressure was increased compared to controls while the levels in classic CAH and controls were similar [47].

In CAH adults, single blood pressure measurements in 29 young patients were normal and equal to controls [91]. In 61 adult CAH females single [8] and in 30 adult CAH males ambulatory 24 h blood pressure measurements [9] were similar to controls. All the patients and controls younger than 30 years of age were normotensive, while among older patients and controls the percentage with high blood pressure or on antihypertensives was similar [8, 9]. In contrast, in a UK national survey ($n = 201$) by Arlt et al. [43], the subgroup of females with classic phenotype demonstrated increased diastolic pressure compared to national data. In 30 untreated SV CAH adult females mainly systolic but also diastolic (trend) blood pressure were elevated [87]. In a recent study by Mooij et al. [90], 24 h ambulatory blood pressure was found to be generally elevated in 27 CAH adults compared to BMI-matched controls.

Heart rate

Raised heart rate is an identified risk factor for cardiovascular and non-cardiovascular death, especially in men, some finding heart rate to be independent of other cardiovascular risk factors [115–117]. Even a slight elevation of the heart rate within the normal range can increase the cardiovascular risk. This is illustrated by a study showing that an increase from 60–70 to 70–80 beats/min increased the absolute risk of all-cause mortality with about 2.5% during 12 years [117]. Heart rate has been found to be normal in young CAH individuals [9, 118–120], but increased in our CAH males ≥30 years compared to controls [9]. The 24 h ambulatory monitoring demonstrated an increased heart rate by 27 beats/min during night and 13 beats/min during day time compared to controls. Heart rate was correlated with other cardiovascular risk factors; decreased testosterone levels and increased HbA1c explained half of the increase. Increased heart rate using 24 h ambulatory monitoring was also found in another

study of adult CAH patients but this time compared to BMI-matched controls [90] explaining a smaller rise.

Intima-media thickness

In 19 young adults with CAH intima-media thickness, a predictor of clinical arteriosclerosis and associated with cardiovascular risk was reported to be increased compared to controls [91]. This is an interesting finding and should be investigated further.

Factors influencing the cardiometabolic profile

Increased cardiovascular risk compared to controls was predominantly found in our CAH individuals above 30 years of age [8, 9, 89], possibly due to a longer lifetime exposure to exogenous glucocorticoids. A change in the medical management by time in our patients may also be of importance. The majority of the older patients were treated in general pediatric care during childhood, but the younger ones have been treated either within or with back-up from pediatric endocrinology units, most likely with a more optimal corticosteroid therapy and access to life-style interventions. Of note is that none of our included patients or controls had undergone neonatal 17OHP screening, the future will show if this could improve cardiometabolic risk further.

It is unknown whether cardiometabolic risk can be associated with the CAH genotype. We studied the three most common *CYP21A2* genotype groups (null, I2 splice, and I172N) and their association to cardiometabolic risk in CAH males and found a significant increase in risk parameters in the less severe genotype I172N compared with the other genotypes [9]. This intriguing suggestion will be further explored.

As previously mentioned, in children the preferred glucocorticoid is hydrocortisone while in adults usually prednisolone is used. Increased cardiometabolic risk was mainly seen in our 8 CAH adult males on hydrocortisone or cortisone acetate when compared with our 18 CAH adult males on prednisolone [9]. The doses of glucocorticoid were similar if hydrocortisone equivalents were calculated. The reason is unknown, but could be due to better compliance and control of androgens with prednisolone [9]. However, no data on the length of time on the different glucocorticoid preparations were available.

Delayed diagnosis is associated with long-term androgen excess which can affect the risk profile negatively. This is supported by a study where NC CAH boys and girls had more parameters of insulin resistance and higher systolic blood pressure compared to controls, which were not seen in classic CAH boys and girls [47]. These NC children were diagnosed on average more than 5 years later than the classic CAH children. For clinical monitoring of cardiovascular risk factors see below.

Tumors

Testicular adrenal rest tumors

During the embryological period the testes and aberrant adrenal cells descend together in most males. These aberrant cells most likely vanish if not stimulated, however, if stimulated, TARTs may arise. TARTs have receptors for both ACTH and angiotensin II, and high levels due to under-treatment of glucocorticoids and mineralocorticoids in CAH can enhance their growth [121]. Their typical location in the rete testis increases the risk of obstruction of the seminal ducts with subsequent permanent testicular damage. TARTs have reported to be present in about 20% of children down to 6 years of age [122, 123], and have even been detected at autopsy in 3 of 7 CAH boys younger than 8 weeks [124]. Only TARTs >2 cm are detectable by palpation due to their location buried within the testis [125]. Ultrasound and MRI revealed TARTs equally well down to a size of 0.2 × 0.2 × 0.2 cm [126]. The highest frequency of TARTs reported has been 94% [127], similarly we found 86% of our CAH males affected [128], while others report prevalences of 0–69%, probably reflecting differences in mode of detection and the age of patients [43, 59, 129–135]. TARTs are considered the most important reason for CAH male infertility [125]. For details on fertility and testicular function see "Male fertility".

It is not always effective to reduce the TART size by suppressing ACTH secretion by intensifying corticosteroid supplementation. Even in well-controlled CAH males with normal or suppressed plasma ACTH levels, TARTs have grown [136, 137]. In fact, hormonal parameters of treatment control were not correlated with TART volume [138]. Consequently, other unknown factors may contribute to tumor growth.

When no decrease of the TARTs can be achieved with increased doses of corticoids, or if there is persistent azoospermia despite tumor reduction, testis-sparing surgery could be considered to improve fertility. Two small case series on steroid unresponsive TARTs have reported good results [136, 139]. However, in eight infertile CAH males with TARTs, gonadal dysfunction and oligo-azoospermia did not recover by surgery suggesting permanent damage of the testicular tissue [140]. The conclusion was that surgery is only indicated for relief of pain and discomfort caused by TART. If surgery is considered for longstanding TARTs, it should only be performed when testicular biopsies have demonstrated viable testicular tissue preoperatively. Thus, surgery to improve fertility is very uncertain. It is important,

however, to increase the awareness among clinicians and pathologists of these benign tumors to prevent unnecessary or chidectomy for suspected malignancy. This is illustrated by a study of CAH adults where 6% (4/65) had previously undergone avoidable unilateral or chidectomy [43], and our CAH males where 7% (2/30) had unnecessary testicular surgery for suspected malignancy [128].

Ovarian tumors

In contrast to TARTs, ovarian adrenal rest tumors (OARTs) are very rare [141]. A recent case report with a review of the literature reported 10 cases of OARTs of which 8 were associated with CAH and 2 with Nelson's syndrome [142]. Suggestions have been made that differences in the ontogenesis of the gonads but not the descent of aberrant adrenal tissue is the cause of the huge disparity in prevalence of TARTs and OARTs [142].

Adrenal tumors

Long-standing elevation of ACTH secretion may lead to adrenocortical hyperplasia [6]. Tumor formation may then take place in the hyperplastic adrenal cortex [143, 144]. Indeed, the prevalence of adrenal tumors detected by computer tomography (CT) or MRI has been reported to range between 11 and 82% [134, 138, 144], with less than a third of the adrenals reported to be normal. Nermoen et al. [134] found in a cohort of 62 CAH patients, seven individuals with adrenal tumors (two with bilateral). Four tumors were myelolipomas. Interestingly, even adrenal hypoplasia was demonstrated in 11% of patients, which may indicate overtreatment with glucocorticoids [134]. The size of both the adrenal and the tumor, correlated positively with current parameters of hormonal control [134, 138]. Not only CAH individuals may have high frequency of adrenal tumors but also 45% of CAH carriers were reported to have adrenal tumors [144]. Manifest CAH and CAH carriers may be overrepresented among patients with adrenal incidentalomas. Using genetic analysis in patients with uni- or bilateral adrenal adenomas 16% were CAH carriers and 2–5% were undiagnosed CAH [145, 146]. We have found a few undiagnosed NC CAH patients in the work-up of adrenal tumors, the oldest being a 88-year-old woman [22]. When tumors are found, conventional evaluation should be performed to exclude other types of tumors that demand treatment. See further "Clinical monitoring".

Pituitary tumors

Under-treatment of glucocorticoids leads to elevated ACTH levels, but sometimes the ACTH levels are increased in spite of supraphysiological doses [6], probably due to unphysiological timing of the doses. One small MRI study of seven CAH patients found three pituitary microadenomas and one empty sella. All the four patients with pituitary pathology were of SW phenotype while those without pathology were all SV phenotype [147]. Bilateral adrenalectomy is occasionally used to control hyperandrogenism in CAH when conventional therapy fails [10, 148]. This often results in ACTH hypersecretion [149], and may further develop into pituitary adenoma and Nelson's syndrome [150].

Clinical outcomes of fertility, pregnancies, and offspring

Female fertility

Low rates of pregnancy among women with CAH has consistently been reported both compared with age-matched controls [35, 151–154], and in relation to the fertility in the actual population [43, 155–157]. Fertility appears less impaired in NC CAH [155, 156]. High rates of miscarriages have, however, been demonstrated in untreated NC [155, 156], even rarely very late ones [158]. In our Swedish cohort of CAH females only 26% had been pregnant compared to 66% of controls [35]. The number of delivered children was less than half in CAH compared to controls (25 vs. 54). An association between the severity of the *CYP21A2* mutation and the fertility rate was clearly demonstrated with no term pregnancy in the null group, 13% in the I2 splice group, 33% in the I172N group, and 50% in the group of mutations consistent with NC CAH [35]. Numerous reasons for the low fertility in CAH women have been proposed: delayed psychosexual development and differences in psychosocial orientation, low sexual activity, adrenal overproduction of androgens and steroid precursors, PCO, neuro-endocrine factors, and genital surgery [151, 159]. However, in our cohort, the main reason for lower fertility was that few lived in heterosexual relationships and few had ever tried to become pregnant. All CAH women who tried to become pregnant had succeeded, sometimes after some medical help, except for a few of the older patients [35]. A UK cohort showed a similar result with 91% delivered if only those who desired pregnancy (24% of the entire cohort) was considered [157]. Adding a mineralocorticoid may help fertility in SW and SV [160]. Homo- and bisexuality is common in women with CAH [33, 35, 159, 161]. A relationship between the severity of the *CYP21A2* mutation and non-heterosexual orientation has been reported by us (Fig. 4). A similar association was found between the genotype and having no partner [33]. The reason for being single may stem from unsatisfactory genital surgery causing both psychosexual

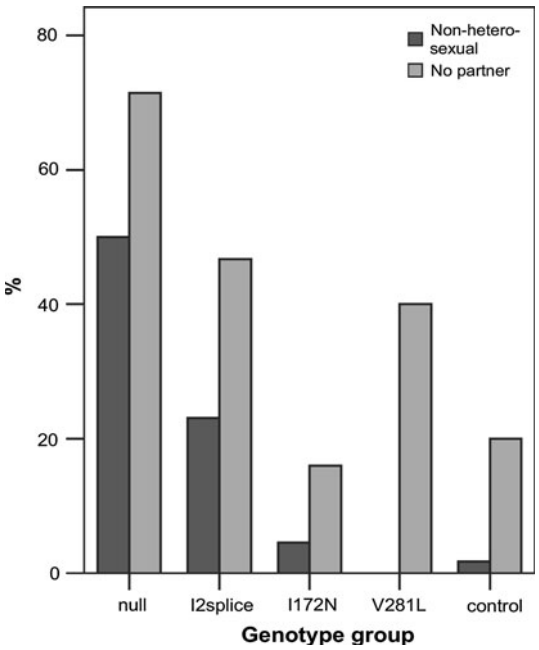

Fig. 4 Bi- or homosexual orientation and having no partner in adult CAH women, divided into different *CYP21A2* genotype groups (null $n = 14$, I2 splice $n = 15$, I172N $n = 25$, V281L $n = 5$) and 62 controls. From Frisen et al. [33]. Copyright 2009, The Endocrine Society

and physical problems. Moreover, CAH females have a need for a certain distance in social and close relations, i.e., detachment [162], in addition to a decreased interest in infants [163].

Outcomes of pregnancies

Pregnancies are usually normal and uneventful in CAH women [35, 153, 157, 159]. We reported, however, gestational diabetes to be about 20% compared to none in controls [8, 35]. Pre-eclampsia has been reported in 0–7% of patients [35, 157, 159], acute or elective caesarean section is common (52–84%) an important reason being previous genital surgery [35, 153, 157, 159]. There is no consensus in recent guidelines, regarding the glucocorticoid doses during pregnancy [10]. Only 12% of our patients needed a dose increase [35], which is in agreement with another report that the majority of women can keep their regular glucocorticoid and mineralocorticoid doses during pregnancy [153]. Dexamethasone should be avoided for maternal adrenal steroid replacement as it is not metabolized by placental 11β-hydroxysteroid dehydrogenase type II [10].

Outcome of the offspring

The outcomes of the offspring are usually excellent. Small for gestational age (SGA) was reported as increased in one study (16% affected) [153]. We found no case of SGA, malformation, or virilization [35]. One case of severe virilization with ambiguous genitalia due to maternal androgen excess has been published [164]. The mother had SV CAH and had ceased glucocorticoid replacement before conception. We discovered the sex ratio to be different with more than thrice the number of girls than boys being born [35], and when combining the reports were the sex of the offspring had been described twice as many girls compared to boys had been born (68 vs. 34)[35, 153, 159, 160, 165]. The explanation is uncertain but one hypothesis is that the hormonal status in CAH mothers at the time of implantation impacts on the uterine milieu favouring female sex in the children [35]. The long-term follow-up of the offspring has shown normal physical and intellectual development [35, 153], however, one boy of a SV mother was diagnosed at 4 years of age with SV CAH [35] and one boy of a NC mother was diagnosed with NC CAH [153]. The risk of a NC CAH mother to have a child with classic CAH is 1.4–2.5% and at least 14.8% will have NC CAH [155, 156]. This extremely high risk is probably explained by including populations where intermarriage within the ethnic subpopulation is frequent and the prevalence of NC CAH is high. Dexamethasone treatment to pregnant CAH women can suppress the fetal androgens and overcome the virilization in female fetuses affected by classic CAH. However, most fetuses will be healthy and there are indications that the therapy may lead to future cognitive impairment with reduced verbal working memory [166]. Larger studies are needed to clarify the potential risks with dexamethasone treatment.

Male fertility

Fertility in CAH males has been reported as being in the range of normal to severely impaired [59, 130]. However, the report on normal fertility is from the 1970s when no genetic confirmation of the diagnosis was available [59]. A recent study from UK reported that 37% of their included CAH males had sought fertility treatment and 67% had been successful with 8% conceiving after fertility treatment [43]. This probably indicates a reduced fertility rate, but no comparison with controls was performed. A Finnish study of CAH males found a child rate of 0.07 compared to 0.34 in the whole Finnish male population with equal age distribution [130], performing similar analysis in our CAH males the figures were 0.9 compared to 1.8 [128]. Although both under-treatment [125] and over-treatment [132] with glucocorticoids can hamper fertility, the frequent occurrence of TARTs is considered the most important reason for reduced fertility, see above [125]. Impaired semen quality is frequent as well as low fecundity [127, 131, 132]. Nevertheless, TARTs may be present in CAH males at the

time of conception. To father a child only one viable sperm is necessary. In one study by Reisch et al. [132] all semen samples were pathological but 22% had fathered children. However, low fertility has been reported in CAH males in spite of the fact that levels of gonadotropins and the marker of active spermatogenesis, inhibin B, were similar to age-matched controls suggesting normal fertility [130]. Thus, sexual and psychosocial factors may, as in CAH women, be of importance for fertility in CAH males. Our clinical practice in monitoring fertility issues in females and males are summarized below.

Clinical outcome of vocal pathology in females

High levels of androgens increase the laryngeal tissue mass with longer and thicker vocal folds leading to lower fundamental frequency of the voice. We have demonstrated that adult CAH women have more problems with their voice in daily life, speak with lower mean, lower minimum and lower maximum fundamental frequency compared to controls [167]. Moreover, the CAH women also demonstrated deeper voice quality compared to controls. The CAH women with a deeper voice had higher BMI and lean body mass compared to the CAH women with normal voice. Voice problems were also associated with late CAH diagnosis and poor compliance, though there were some CAH women who had a normal voice in spite of late diagnosis and incomplete compliance [167].

Summary of clinical management of CAH adults

The following outlines are based on the evidence presented above or where such evidence is lacking our own and others' clinical experience.

1. Ideally, adult CAH women and men should be regularly seen, at least yearly, by a CAH experienced endocrinologist and CAH women also by a CAH experienced gynecologist. Males may need andrological expertise. Psychiatrists and psychologists with insights in the specific problems of CAH are valuable resources as well as phoniatric support. The build-up of such a team demand centralization of the CAH care.
2. *CYP21A2* mutation analysis is of value for all the CAH individuals to confirm the diagnosis and for classification into the different genotypes.
3. It is generally recommended that all classic CAH patients should receive glucocorticoids while NC CAH patients only if symptomatic. Hydrocortisone and prednisolone are the favoured glucocorticoids. Prednisolone may be preferred due to better compliance, usually 2.5–7.5 mg/day divided into two doses. Monitoring of serum androstenedione, testosterone, SHBG and morning 17OHP or diurnal 17OHP curve with dried blood spots (our preference) can be used to adjust doses.
4. Fludrocortisone is generally mandatory in SW, but is also recommended in SV as it allows management with lower doses of glucocorticoids. Fludrocortisone can occasionally been used in NC. The aim should be to keep plasma renin or plasma renin activity in the range from mid-normal to slightly elevated. Usually doses around 0.1 mg are employed but older adults normally benefit of lower doses (0.05–0.025 mg) due to side-effects.
5. Our yearly check-ups include measurements of height, weight, BMI, waist-to-hip ratio, blood pressure, heart rate, and plasma glucose. Pathological results are treated conventionally. A healthy life-style is encouraged.
6. DXA measurements of BMD are carried out when the patients is transferred from pediatric to adult care and depending on the BMD levels and the patient's individual risk, and fracture occurrence, repeated suggestively every second to fifth year. Osteopenia and osteoporosis are handled as generally recommended.
7. In CAH males, we document the presence of TARTs regularly from young adult age by clinical examination and ultrasound or MRI along with check-up of gonadotropins, testosterone, SHBG. Inhibin B measurements or semen analysis is considered if multiple and/or large TARTs are present. The patients should be informed of the risk of declining fertility by time but also that TARTs are benign.
8. In CAH females we monitor their menstrual cycle. During pregnancy the patients undergo regular antenatal supervision and screening for gestational diabetes, preferably with oral glucose tolerance test. A more careful follow-up of the offspring than routine may be considered, especially in certain ethnic subpopulations where intermarriage is common and a high frequency of NC CAH is present. Genotyping of the partners of NC CAH women may also need to be considered, especially if one severe mutation is present to offer genetic counselling.
9. When ovarian, adrenal, and pituitary tumors are detected as incidentalomas we carry out conventional evaluation to exclude other types of tumors that demands treatment. Optimizing glucocorticoid therapy may arrest growth of tumors and prevent new ones from arising. Diagnostic work-up of ovarian, adrenal, and pituitary tumors is only performed in case of clinical signs and symptoms.

10. In women, monitoring of the voice is considered if subjective and/or objective voice problems are noted and may be avoided by keeping androgens within normal ranges. Avoiding high androgens may prevent future voice trouble. Voice training guided by a trained speech therapist can ameliorate symptoms.

Future perspectives

More optimal glucocorticoid and mineralocorticoid treatments with better monitoring, new preparations and delivery formats which allow for a more physiological replacement will hopefully lead to better clinical outcomes for CAH individuals. Moreover, the introduction of neonatal CAH screening may also further improve outcomes. An area of future research is the relative importance of genotype and phenotype in prediction of clinical outcomes. At present certain genotype characteristics have been found in females with the null mutation and in males with the I172N mutation but larger materials need to be studied. In the more distant future, the ultimate goal which is cure may be feasible with gene therapy.

Conclusion

CAH is a complex disorder which may lead to many negative clinical outcomes such as impaired QoL, short stature, osteoporosis and fractures, increased cardiometabolic risk, benign adrenal and testicular tumors, decreased fertility, and voice problems. Classifying patients according to genotype may give additional useful clinical information, especially to identify females with the null mutation. Consequences of CAH may have been milder during the last decades thanks to better clinical management and nowadays most affected patients seem to have a good QoL. The introduction of neonatal CAH screening may enhance long-term results. Monitoring of different risk factors and negative consequences should be done regularly in an attempt to improve clinical outcomes further. However, more studies are needed as published studies have been relatively small and few older patients have been included, partly due to the late introduction of glucocorticoids in the 1950s.

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