Hormonal treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Available online 08 August 2007

Abstract

During childhood, the main aims of the medical treatment of congenital adrenal hyperplasia (CAH) secondary to 21-hydroxylase deficiency, are to prevent salt loss and virilization and to achieve normal stature and normal puberty. As such, there is a narrow therapeutic window through which the intended results can be achieved. In adulthood, the clinical management has received little attention, but recent studies have shown the relevance of long-term follow-up of these patients. Indeed, long-term evaluation of adult CAH patients enables the identification of multiple clinical, hormonal and metabolic abnormalities as bone mineral density alteration, overweight and disturbed reproductive functions. In women with classic CAH, low fertility rate is reported, and is probably the consequence of multiple factors, including neuroendocrine and hormonal factors, feminizing surgery, and psychological factors. Men with CAH may present hypogonadism either through the effect of adrenal rests or from suppression of gonadotropins resulting in infertility. These patients should therefore be carefully followed-up, from childhood through to adulthood, to avoid these complications and to ensure treatment compliance and tight control of the adrenal androgens, by multidisciplinary teams who have knowledge of CAH.

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Keywords: Adrenal rest tumours; Body mass index; Bone mineral density; Congenital adrenal hyperplasia; Fertility; 21-OH deficiency

1. Introduction

Congenital adrenal hyperplasia (CAH MIM 201910) describes a group of inherited autosomal recessive disorders characterized by enzyme defects in the steroidogenic pathways that leads to the biosynthesis of cortisol, aldosterone and androgens. The relative decrease in cortisol production acting via the classic negative feedback loop, results in the increased secretion of ACTH from the pituitary gland and to subsequent hyperplasia of the adrenals (Fig. 1A,B) [1]. Deficiency of the 21-hydroxylase enzyme is the most common form of CAH, accounting for more than 95% of cases and is one of the most common known autosomal recessive disorders. 21-Hydroxylase is a cytochrome P450 that catalyses the conversion of 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol (Fig. 1C). Cortisol deficiency results in the ACTH-induced accumulation of substrate precursors such as 17OHP and progesterone, and to increased secretion of adrenal androgens, especially androstenedione [1]. The same enzyme is also required for mineralocorticoid production, which deficiency leads to impaired synthesis of aldosterone [1] CAH due to 21-hydroxylase deficiency is the result of deletions or deleterious mutations of the active gene CYP21. Duplicated 21-OH genes, an active gene CYP21 and a pseudogene (CYP21P) are located on chromosome 6p, within the major human histocompatibility complex, about 30 kb apart, adjacent to and alternating with the C4B and C4A genes encoding for the fourth component of serum complement [2,3]. Many different mutations of the CYP21 gene have been identified causing varying degrees of impairment of 21-hydroxylase activity that result in a spectrum of disease expression [4]. Most patients are compound heterozygotes, and the clinical phenotype is generally related to the less severely mutated allele and, consequently, to the residual 21 hydroxylase activity.
Indeed, CAH is classified according to symptoms and signs and to age of presentation. The clinical phenotype is typically classified as classic, the severe form, or non-classic (NCF), the mild or late-onset form. Classic CAH is subclassified as salt-wasting (SW) or simple-virilising (SV) forms, reflecting the degree of aldosterone deficiency. Several studies have suggested high concordance rates between genotype and phenotype in patients with classic form of CAH, but less observed in NCF patients. Classical disease occurs in approximately 1/15 000 births, while the NCF occurs in approximately 1% of the general population, many of them being undiagnosed [5]. The lives of patients with CAH have improved greatly since the discovery, in the 1950s, that cortisone was an effective treatment for the disorder. Neonatal screening is being done in several countries, and gene-specific prenatal diagnosis is now feasible [6]. Current treatment is intended to reduce excessive ACTH and consequent increase in androgen production by substituting for deficient cortisol synthesis and, when necessary, aldosterone deficiency, to ensure normal fertility, and to avoid the long-term consequences of glucocorticoid use. In such an intervention, there is a narrow therapeutic window through which the intended results can be achieved.

2. Transition from childhood to adulthood

2.1. Treatments

Substitution therapy with glucocorticoids is offered in an attempt to suppress the excessive secretion of CRH and ACTH by the hypothalamus and anterior pituitary, respectively, and to reduce the circulating concentrations of adrenal androgens and androgen precursors. The preferred glucocorticoid option is hydrocortisone, because its short half-life minimizes growth suppression as well as other adverse side effects of more potent, longer-acting glucocorticoids. One study had suggested that in patients with classic 21-hydroxylase deficiency, hydrocortisone replacement therapy should be administered during the period of increased hypothalamic-pituitary-adrenal activity, i.e. between 04.00 and 16.00 h [7]. The highest hydrocortisone dose should be given in the morning, because circulating cortisol concentrations obtained after evening doses are likely to be undetectable by the time of the rapid rise in 17OHP concentrations at 04.00 h. Blood investigations performed as part of monitoring of CAH patients should include androstenedione, testosterone and 17OHP concentrations obtained in the morning before the oral dose of hydrocor-
sample is to be obtained [8]. However, it is important to note that there is actually no consensus on treating adults, concerning the type of glucocorticoids, the use of a reverse circadian pattern of glucocorticoid treatment, or the use of a dose based on weight or surface area. In a recent study, some authors have demonstrated that the most important variable determining hydrocortisone bioavailability is weight; therefore, the authors advocated a weight-related dosing regimen [9]. Furthermore, there is no established cut-off of 17OHP levels in adults, and the optimal dose of glucocorticoids is that which fails to fully suppress 17-hydroxyprogesterone and maintains androgens in the mid-normal range.

Mineralocorticoid treatment should be keeping on in patients with SW form and is achieved with fludrocortisone. The dose should be adjusted to avoid hypertension and to maintain plasma renin activity in the upper normal range, although there is no consensus on the exact therapeutic goal of this treatment in adult patients. The use of fludrocortisone therapy in patients with simple virilizing form of CAH should be recommended because it might allow management with lower doses of glucocorticoids [5,10].

2.2. Bone mineral density

Osteoporosis has been an understandable concern for adults with CAH who may receive or have received supraphysiologic doses of glucocorticoids. Some previous reports on bone mineral density (BMD) in adult CAH patients showed no significant differences in BMD between patients with CAH and controls as measured by dual energy X-ray absorptiometry (DXA) [11–16], but others have found lower BMD Z-scores in all or certain subpopulations of CAH patients [17–24]. These reports differ with respect to age selections and glucocorticoid regimens. In reports documenting the BMD reduction, this outcome has been attributed to an accumulated effect of prolonged exposure to excess glucocorticoids during infancy and childhood. The role of each of these factors has been evaluated in a number of studies published over the last decade, often with conflicting results. Most studies are retrospective, include mixed populations (children and young adults), have a small sample size, and are unable to precisely assess the effect of cumulative glucocorticoids doses. Moreover, only two studies included patients older than 50 years [17,19]. In our population, including 45 adult patients, we found that osteopenic subjects had higher hydrocortisone doses than subjects with normal BMD [24]. This was in agreement with recent reports, which had also demonstrated lower BMD in adult CAH patients, attributing the decrease to excessive cortisol replacement [17,18,22]. Their participants had significantly lower lumbar and femoral neck BMD scores than controls. Studies conducted in subjects under glucocorticoid treatments have shown that long-term treatment may induce osteoporosis, with biochemical evidence of decreased bone turnover and bone loss occurring principally within the first 6 months of treatment [17,25]. It is also possible that 25-hydroxyvitamin D deficiency, induced by glucocorticoids, observed in 44% of our patients plays a role in the decreased BMD. Therefore, Vitamin D status should systematically be determined in CAH patients and calcium and Vitamin D supplementation should be recommended in patients with Vitamin D deficiency and those receiving high dose of steroids. A recent study suggests an association between oversuppression of adrenal androgen and decreased BMD in adult CAH women [22]. Finally, some studies suggest that higher BMI may offer some protection against bone density loss in adult patients with CAH [24]. Biochemical markers of bone turnover have also been evaluated in patients with CAH [11,15,23]. Bone turnover was lower in patients with CAH than in controls, and osteocalcin levels correlated positively with growth velocity and negatively with BMD [11,15]. Another recent study showed higher bone-specific alkaline phosphatase and type I collagen C-terminal telopeptide concentrations in CAH patients compared with control subjects, but this did not correlate with the actual glucocorticoid dose or the mean dose using during the previous 7 years [23]. Despite these conflicting results, and because some studies showed that young adult patients with the classical form of CAH have decreased bone density values compared with healthy controls and that this may put them at risk for developing osteoporosis early in life, we recommend to check systematically BMD in CAH adult patients. The frequency of such measure during adulthood remains unresolved, and probably depends on the initial result of the BMD.

2.3. Metabolism

Body mass index (BMI) is found to be elevated in most [17,19,24,26], but not all [11,18], reports on CAH patients. One study has shown an increased risk of obesity among children and adolescents with classic CAH due to 21-hydroxylase deficiency, compared with a reference population [27]. There was a slight but significant positive correlation of BMI with the current hydrocortisone dosage of the patients. Moreover, fat mass measurements by DXA seem to be elevated in young CAH adults [14,16,18]. We also recently reported increased BMI in our CAH population, as in other studies, and a significantly positive correlation between an insulin resistance index, HOMA, and BMI, and between HOMA and 17OHP levels, which persisted after adjusting on BMI [24]. Another recent study showed higher insulin levels in the CAH women above 30 years compared with controls. Moreover, the authors reported a high frequency of gestational diabetes among these patients, indicating potentially a higher risk to develop diabetes in a near future [28]. In another study, an increased intima-media thickness has been reported suggesting there is a need for long-term follow up and further studies of determination of the cardio-vascular risk in CAH [29]. Indeed, some authors have shown that hyperandrogenemia could be an independent
risk factor for hyperinsulinism in adolescent girls and in women [30,31]. This is consistent with a study of untreated non-classical 21OHD young women, who were demonstrated to be significantly less sensitive to insulin than control subjects [32]. On the other hand, this insulin resistance may expose these CAH women to an increased risk for developing polycystic ovaries, then enhancing androgen production, and the cardiovascular risk of insulin resistance. Recently, Charmandary et al. reported significantly higher BMI values together with elevated serum leptin and insulin levels and increased insulin resistance index and reduced catecholamine levels in 18 children with CAH, compared with healthy control subjects [33]. The authors of this study explain this difference by long-term differences in adrenomedullary function, androgen concentrations and exposure to glucocorticoids. Further studies are needed to determine the regulation of insulin and glucose in patients with CAH, who may benefit from prevention and treatment of their potential insulin resistance. Another important cardiovascular risk factor is hypertension. The prevalence of hypertension in adults with 21-hydroxylase deficiency has not yet been reported, but in children and adolescents, Roche et al. found that 58% had increased systolic and 24% had increased diastolic blood pressure when measuring 24-h ambulatory blood pressure [34]. Moreover, other data show altered 24-h blood pressure profiles with elevated systolic levels, which correlate with the degree of overweight and obesity [35]. Finally, to date, reports on cardiovascular morbidity and mortality in patients with classic CAH are lacking.

2.4. Fertility and reproductive axis in CAH women

Reduced fertility has been reported in patients with classic and non-classical CAH, especially in SW women [36–39]. The most important study was done in 1987 and had included 80 CAH women [36]. Half of these women did not have sexual activity and among those with sexual activity, fertility rate was low. Among 25 women with SV form and adequate vaginal opening, fertility rate was 60%, meanwhile among the 15 women with SW form with adequate vaginal opening, fertility rate was only 7%. However, more recent data suggest that fertility rates have significantly improved, from 60% in SW patients to 80% in SV patients [37], largely owing to earlier treatment of CAH, improvement of compliance with therapy and surgical advances in genital reconstruction leading to increased percentage of patients with sexual activity [37–40].

Several factors have been suggested to contribute to the disturbed reproductive axis in CAH females: adrenal overproduction of androgens and progesterone, ovarian hyperandrogenism, neuroendocrine factors, feminizing surgery, and psychological factors such as reduced sexual activity and low maternal feelings. Indeed, several hormonal factors might play a role: aromatization of excess adrenal androstenedione and hypersecretion of progesterone might interfere with LH and FSH secretion [41,42]. Elevated progesterone or other sex steroids levels could induce abnormal ovarian function by programming the hypothalamus early in development [43] and inducing hypersecretion of LH at puberty. Androgen excess might directly damage the ovaries. Deficient 21-hydroxylation of progesterone in the zona glomerulosa of salt-wasting patients may lead to a further increase of adrenocortical progesterone secretion, causing elevated levels during follicular phase. This adrenal progesterone can prevent thickening of the endometrium in the follicular phase. This may also occur in well substituted or oversubstituted patients, as shown in one study, due to the gestational potency of 17OHP that has been reported to be 1% that of progesterone [41,42]. Menstrual irregularities, from oligomenorrhea to amenorrhea, are frequent in CAH women and they are estimated to be present in 64 to 68% of SW women and 55 to 75% of SV women. Hirsutism is present in 20 to 30% of the patients [36,37]. Due to the role of multiple hormonal factors, the regularity of menstrual cycle can be considered as an important measure of therapeutic control in women with CAH. The relation between obesity, hyperandrogenism, insulin resistance, and the development of polycystic ovaries in CAH requires further study.

The second factor implicated in the reduced fertility of the CAH women is the feminizing surgery. Obviously, there is a relationship between sexual activity and vaginal function [36]. There are few long-term follow-up studies evaluating the outcome of surgery in CAH women, and most of those studies have small sample sizes. Genital surgery and especially the timing of vaginoplasty has been a matter of debate. Long-term aims of this surgery are to allow normal looking and functioning adult female genitalia. One recent study showed that despite the poor outcome of the initial single-stage surgery in infancy, and the reoperation in puberty in most of the patients due to vaginal stricture or vaginal stenosis, the adult outcome [44] seems more positive than the findings in the few previous reports, especially with respect to sexual development and activity. Nevertheless, three recent studies have shown impaired sexual function in CAH women who previously had genital surgery, potentially related to the compromised sensitivity and restricted intromits [45–47]. Data on the youngest adult generation who may have benefited from improved insights in surgical methods are needed, especially with respect to adult sexual function and patient’s satisfaction with the treatment. All these data also underscore the importance of psychological support in the treatment of children with CAH.

Finally, some psychological factors can explain the reduced fertility. Studies of female patients with classic CAH suggest that exposure to excess androgens during prenatal development influences brain development. Indeed, female patients with classic CAH have been found to have more male-typical childhood play than unaffected girls, are more likely to use physical aggression in conflict situations and have less interest in infants and nurturing activities [5]. Nevertheless, recent studies have shown that these women have normal sexual identification, and do not have gender identity confusion [48]. Sexual preference has been studied, but the results are conflicting, with a large variability of heterosexuality and homosexuality rates probably due to the different methods of these studies.
Analogous to testicular adrenal rest tumours, ovarian adrenal rest tumours have been described, but only in case reports [49–51]. It is very likely that ovarian adrenal rest tumours, if present, could impair ovarian function in CAH females by displacing normal ovarian tissue and by locally producing steroids, which interfere with normal ovarian function. Systematic study of ovarian adrenal rest tumours by pelvic ultrasonography and MRI was not able to detect them in any of the 13 CAH women studied, according to the diagnostic criteria derived from the imaging features of testicular adrenal rest tumours [52]. This suggests that ovarian adrenal rest tumours in CAH females are rare, in contrast to the high prevalence of testicular adrenal rest tumours in CAH males.

Successful pregnancy outcomes are possible in women with classic CAH, and careful management during gestation is indicated, especially if the fetes are female [for review see53]. In pregnant women with 21-hydroxylase deficiency, glucocorticoids that are inactivated by placental 11β-hydroxysteroid dehydrogenase type II (i.e. hydrocortisone, prednisone) are recommended, to minimize fetal adrenal suppression. Dexamethasone, which provides longer and more effective suppression of adrenal androgen production, is transferred across the placenta without oxidation of the 11-hydroxy1 group and can suppress the fetal adrenal gland [54,55], and this treatment should be reserved to pregnancies where the fetus is at risk for congenital adrenal hyperplasia.

2.5. Fertility and reproductive axis in CAH men

Male patients with CAH may present impaired gonadic function and infertility. However, the majority of long-term follow-up data concerns the female patients. It appears that adult males with CAH face a dual problem: adrenal steroid overproduction, especially androgen and progesterone, might interfere with FSH and LH production, resulting in gonadotropin deficiency and consequent small testicular size and infertility [56,57], whereas adrenal rests can destroy the testicular tubules and lead to infertility or may interfere directly with the function of normal testicular tissue in a mechanical way or by local steroid production. Optimal control of adrenal steroid secretion appears then to be crucial to preserve fertility in adult males with CAH. However, there is no sufficient long-term hormonal data to determine the role of treatment of CAH in the prevention of gonadic abnormalities.

Testicular adrenal rest tumours in CAH due to 21-hydroxylase deficiency have been described since many years but they have been only recently carefully investigated [56,57]. It is believed that these testicular tumours in CAH patients originate from aberrant adrenal tissue. Biochemical studies in vitro and in vivo support this hypothesis by showing adrenal specific 11β-hydroxysteroids in the testicular tumours [58]. These testicular adrenal rest tumours seem to be ACTH dependent, since they develop during periods of sustained elevation of ACTH and decrease in size during the administration of glucocorticoids [59]. Nevertheless, some studies report the development of testicular tumours despite good hormonal control, suggesting that undertreatment is not the only cause of prevalence of testicular tumours in these patients [56,57]. Such tumours can be misdiagnosed as Leydig cells tumours. However, unlike Leydig cell tumours, they are mostly often bilateral, occur in men with poor adrenal suppression, and decrease in size with increased glucocorticoid suppression [1]. In case of doubt, a biopsy needs to be considered, but this had to be uncommon. Conflicting results exist concerning the prevalence of such tumours, ranging from 30 to 95% of the patients, depending on selection of patients and methods of detection (clinical examination or ultrasonography) [1,56–58]. Furthermore, their impact on fertility has not been yet completely established. Testicular function, both semen production and testosterone secretion, may be impaired in these patients, especially when large testicular tumours are present [56,57]. Indeed, a study has shown testicular dysfunction, with decreased levels of plasma testosterone, in 6 of the 17 patients studied, whereas poor semen quality was demonstrated in 7 among 11 patients [57]. The preferred method of treatment of testicular adrenal rest tumours in patients with CAH is intensifying glucocorticoid therapy. This may lead to decrease of tumour size and improvement of testicular function. If the testicular size is not reduced after suppression therapy or a side effect of glucocorticoid dose is noted, surgical intervention is often considered. However, it is usually associated with a worsening of testicular function [59,60]. A recent study has shown that testis-sparing surgery did not improve pituitary–gonadic hormonal function and semen analysis despite successful removal of the tumours in 8 CAH men [60]. Further studies are needed to evaluate the consequence of such surgery at an earlier stage of the natural history of adrenal rest tumours. We have recently evaluated whether long-term mitotane treatment was able to improve adrenal rest tumours in 3 adults patients with classical CAH since intensification of the glucocorticoid treatment was inefficient or impossible due to major side effects. We observed an improvement of sperm count, testicular adrenal rest tumours size and hormonal gonadic function after 24 to 36 months of mitotane treatment [61]. Nevertheless, this has to be confirmed on a larger series and raises several questions, especially the duration of treatment, the relapse of adrenal rest tumours after mitotane withdrawal, and the impact of mitotane on sperm.

Early detection and treatment of testicular adrenal rest tumours should be of primary concern in men with CAH, by regular testicular examination and ultrasonography. Ultrasound findings include hypoechogenic lesions with hyperechogenic reflections, most often adjacent to the mediastinum testis [62]. Moreover, semen analysis should be performed in these patients. Finally, it seems prudent for many adult endocrinologists to propose systematic semen cryopreservation.

In conclusion, CAH patients should be carefully followed-up, from childhood to adulthood, by multidisciplinary teams who have knowledge of CAH (Table 1). Nevertheless, most studies represent only one window in time. Prospective studies, in a European Network, are needed to better understand the adult consequences of CAH, especially the natural history of
### Table 1
Potential long-term consequences of CAH and suggested follow-up of the patients

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<td>Infertility (Male)</td>
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the disease, the impact of long-term glucocorticoid replacement on bone health and the impact of overweight, which may be associated with metabolic syndrome, on increased vascular risk. This approach could define the future guidelines of care of children with CAH, in order to prevent long-term consequences of CAH.

### Acknowledgements

Zeina Chaktoura is recipient of a grant from the “Association Sarrênales”.

A French version of this article is available at doi: n° DOI de l’article correspondant français.

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