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Congenital adrenal hyperplasia due to 21-hydroxylase deficiency — management in adults

Wrodzony przerost nadnerczy z niedoboru 21-hydroksylazy — problemy i postępowanie u dorosłych

Urszula Ambroziak[1], Tomasz Bednarczuk[1], Maria Ginalska-Malinowska[2], Ewa Maria Małunowicz[3], Barbara Grzechocińska[4], Paweł Kamiński[4], Leszek Bablok[4], Jerzy Przedlacki[5], Ewa Bar-Andziak[1]

[1]*Department of Internal Diseases and Endocrinology, Warsaw Medical University, Poland*
[2]*Department of Metabolic Disorders, Endocrinology, and Diabetology, Children's Memorial Health Institute, Warszawa, Poland*
[3]*Department of Biochemistry and Experimental Medicine, Children's Memorial Health Institute, Warszawa, Poland*
[4]*First Department of Obstetrics and Gynaecology, Warsaw Medical University, Poland*
[5]*Department of Nephrology, Dialysis Therapy, and Internal Diseases, Warsaw Medical University, Poland*

Abstract

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is one of the most common autosomal recessive hereditary diseases. The impairment of cortisol synthesis leads to excessive stimulation of the adrenal glands by adrenocorticotropic hormone (ACTH), adrenal hyperplasia, and excessive androgen synthesis. The syndrome is characterised by a considerable correlation between the genotype and the phenotype with the type of *CYP21A2* gene mutation affecting the severity of 21-hydroxylase deficiency.

The clinical manifestations of CAH in adults result from adrenocortical and adrenomedullary insufficiency, hyperandrogenism, and the adverse effects of glucocorticosteroids used for the treatment of the condition. Non-classic CAH may sometimes be asymptomatic.

In patients with classic CAH obesity, hyperinsulinaemia, insulin resistance, and hyperleptinaemia are more often seen than in the general population. These abnormalities promote the development of metabolic syndrome and its sequelae, including endothelial dysfunction, and cardiovascular disease. Long-term glucocorticosteroid treatment is also a known risk factor for osteoporosis.

Patients with CAH require constant monitoring of biochemical parameters (17a-hydroxyprogesterone [17-OHP] and androstenedione), clinical parameters (body mass, waist circumference, blood pressure, glucose, and lipids), and bone mineral density by densitometry.

The principal goal of treatment in adults with CAH is to improve quality of life, ensure that they remain fertile, reduce the manifestations of hyperandrogenisation in females, and minimise the adverse effects of glucocorticosteroid treatment.

Patients with classic CAH require treatment with glucocorticosteroids and, in cases of salt wasting, also with a mineralocorticosteroid. Radical measures, such as bilateral adrenalectomy, are very rarely needed.

Asymptomatic patients with non-classic CAH require monitoring: treatment is not always necessary.

Medical care for patients with CAH should be provided by reference centres, as the management of such patients requires collaboration between an endocrinologist, diabetologist, gynaecologist, andrologist, urologist, and psychologist.

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Key words: *congenital adrenal hyperplasia, 21-hydroxylase, glucocorticosteroids*

Streszczenie

Wrodzony przerost nadnerczy (CAH, *congenital adrenal hyperplasia*) z niedoboru 21-hydroksylazy jest jedną z najczęstszych chorób dziedziczonych w sposób autosomalny recesywny. Upośledzenie syntezy kortyzolu doprowadza do nadmiernej stymulacji nadnerczy przez ACTH, przerostu nadnerczy i nadmiernej syntezy androgenów. Zespół ten cechuje się dużą korelacją pomiędzy genotypem i fenotypem — rodzaj mutacji genu *CYP21A2* wpływa na stopień niedoboru 21-hydroksylazy.

Objawy kliniczne w klasycznych postaciach CAH u dorosłych wynikają z: niedoczynności kory i rdzenia nadnerczy, hiperandrogenizmu oraz działań ubocznych stosowanych w leczeniu glikokortykosteroidów. Postać nieklasyczna może czasem przebiegać bezobjawowo.

U pacjentów z klasyczną postacią CAH częściej niż w normalnej populacji stwierdza się otyłość, hiperinsulinizm i insulinooporność oraz hiperleptynemię. Nieprawidłowości te sprzyjają rozwojowi zespołu metabolicznego i jego konsekwencjom, w tym dysfunkcji śródbłonka i rozwojowi chorób sercowo-naczyniowych. Przewlekłe leczenie glikokortykosteroidami jest także znanym czynnikiem ryzyka rozwoju osteoporozy.

Chorzy z CAH wymagają stałego monitorowania zarówno parametrów biochemicznych (17-OHP i androstendionu), jak i klinicznych (kontrola masy ciała, pomiary obwodu talii, ciśnienia tętniczego, glikemii, lipidogramu) oraz densytometrycznej oceny gęstości mineralnej kości.

Podstawowym celem leczenia dorosłych chorych z CAH jest poprawa jakości życia, zapewnienie płodności, zmniejszenie objawów hiperandrogenizacji u kobiet oraz minimalizacja objawów niepożądanych glikokortykosteroidoterapii.

Urszula Ambroziak M.D., Department of Internal Diseases and Endocrinology, Warsaw Medical University, Banacha St. 1a, 02–097 Warszawa, tel.: +48 22 599 28 77, mobil: +48 601 229 027, fax: +48 22 599 19 75, e-mail: umak@amwaw.edu.pl

Pacjenci z postacią klasyczną wymagają leczenia glikokortykosteroidami, a w przypadkach przebiegających z utratą soli także mineralokortykosteroidem. Niezwykle rzadko konieczne jest zastosowanie radykalnego postępowania, jakim jest obustronna adrenalektomia. Pacjenci z postacią nieklasyczną, z brakiem objawów klinicznych wymagają obserwacji, leczenie natomiast nie zawsze jest konieczne. Opieka nad dorosłymi chorymi z CAH powinna być prowadzona w ośrodkach referencyjnych, ponieważ wymaga współpracy endokrynologa, diabetologa, ginekologa, androloga, urologa i psychologa. **(Endokrynol Pol 2010; 61 (1): 142–155)**

Słowa kluczowe: *wrodzony przerost nadnerczy, 21-hydroksylaza, glikokortykosteroidy*

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List of abbreviations

AA — Antiandrogens
ACTH — Adrenocorticotropic hormone
ART — Adrenal rest tumour
BMD — Bone mineral density
CAH — Congenital adrenal hyperplasia
GCS — Glucocorticosteroids
CRH — Corticotropin-releasing hormone
DHEA — Dehydroepiandrosterone
DHEAS — Dehydroepiandrosterone sulphate
DXA — Dual energy X-ray absorptiometry
DXM — Dexamethasone
EBM — Evidence-based medicine
GC/MS — Gas chromatography/mass spectrometry
3β-HSD2 — Type II 3β-hydroxysteroid dehydrogenase
11β-HSD2 — Type II 11β-hydroxysteroid dehydrogenase
GH — Growth hormone
IFG — Impaired fasting glucose
IGF-1 — Insulin-like growth factor-1
IGT — Impaired glucose tolerance
IMT — Intima-media thickness
LA GCS — Long-acting glucocorticosteroids
MCS — Mineralocorticosteroids
MRI — Magnetic resonance imaging
NC CAH — Non-classic congenital adrenal hyperplasia
OC — Oral contraceptives
17-OHP — 17α-hydroxyprogesterone
PCOS — Polycystic ovary syndrome
PRA — Plasma renin activity
SD — Standard deviation
SHBG — Sex hormone binding globulin
SV CAH — Simple virilising congenital adrenal hyperplasia
SW CAH — Salt-wasting congenital adrenal hyperplasia
THAldo — Tetrahydroaldosterone

Introduction

Congenital adrenal hyperplasia (CAH) belongs to a group of cortisol synthesis abnormalities inherited as an autosomal recessive trait. The most common form of CAH (accounting for 95% of the cases) is CAH due to 21-hydroxylase deficiency. Mutations of the *CYP21A2* gene, which encodes for the enzyme 21-hydroxylase in the zona fasciculata and zona glomerulosa of the adrenal cortex, result in cortisol deficiency and, if severe, in aldosterone deficiency. This results in stimulation of ACTH release and an excessive formation of these steroids upstream of the blocked stage of synthesis, namely 17α-hydroxyprogesterone (17-OHP), which undergoes excessive conversion to androgens [1, 2]. Figure 1 shows a diagram of adrenal and gonadal steroidogenesis together with the abnormalities caused by 21-hydroxylase deficiency in CAH.

Three main types of CAH are distinguished depending on the severity of 21-hydroxylase deficiency:

— **Classic salt-wasting CAH (SW CAH) —** complete lack of 21-hydroxylase activity in zona fasciculata and zona glomerulosa of the adrenal cortex leading to cortisol and aldosterone deficiency.
— **Classic simple virilising CAH (SV CAH) —** only 1–2% of 21-hydroxylase activity is preserved. Cortisol deficiency is present but no clinical manifestations of aldosterone deficiency are observed.
— **Non-classic CAH (NC CAH) —** late-onset adrenal hyperplasia accompanied by a mild androgen excess in late childhood or during puberty with 20–50% of 21-hydroxylase activity being preserved.

Based on neonatal screening available in such countries as the United States, Portugal, the United Kingdom, Canada, or Spain, the mean prevalence of classic CAH has been established at about 1 in 15,000 live births. The prevalence is much higher in some ethnic groups, for instance, 1 in 280 among the Yupik Eskimos inhabiting Alaska and 1 in 2100 among the inhabitants of the French island Reunion. In Poland CAH is not included in any of the screening programmes and its prevalence is estimated at about 1 in 10,000 to 1 in 14,000 live births [3]. Of the classic forms, SW CAH predominates in all the assessed populations, accounting for 67% of cases [4].

Non-classic CAH is more common (about 1 in 1000 cases) [5]. As with classic CAH, here the prevalence in certain ethnic groups is much higher, namely among Ashkenazy Jews (1 in 27), Spaniards (1 in 40), and Croats (1 in 50) [6].

Clinical manifestations of congenital adrenal hyperplasia in adults

The clinical manifestations of the classic forms of CAH are very diverse and result from the varying degrees

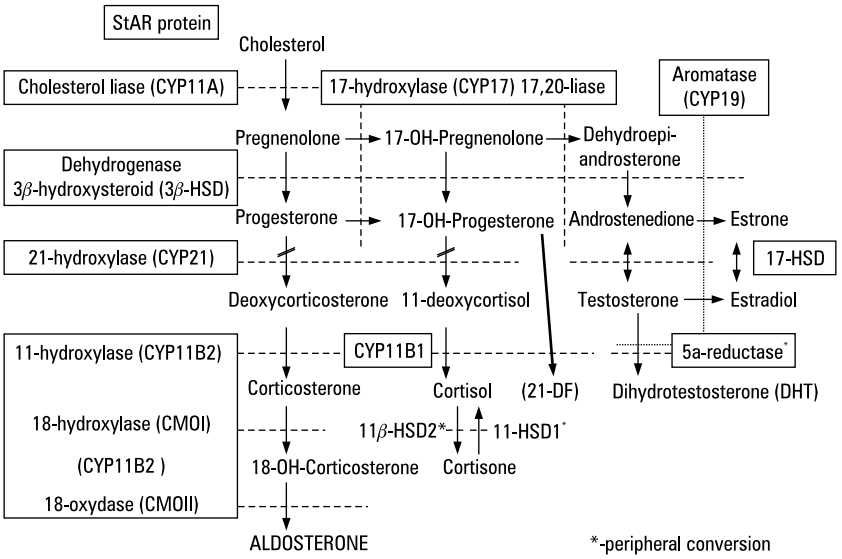

Figure 1. *Pathway of adrenal and gonadal steroidogenesis in 21-hydroxylase deficiency. Modified by EM. Małunowicz from M. New [3]; 21-DF — 21-deoxycortisol*

Rycina 1. *Schemat biosyntezy steroidów w nadnerczach i gonadach, pokazujący zmianę jej szlaku w CAH z niedoboru 21-hydroksylazy. Według M. New, w modyfikacji EM. Małunowicz [3]; 21-DF — 21-deoksykortyzol*

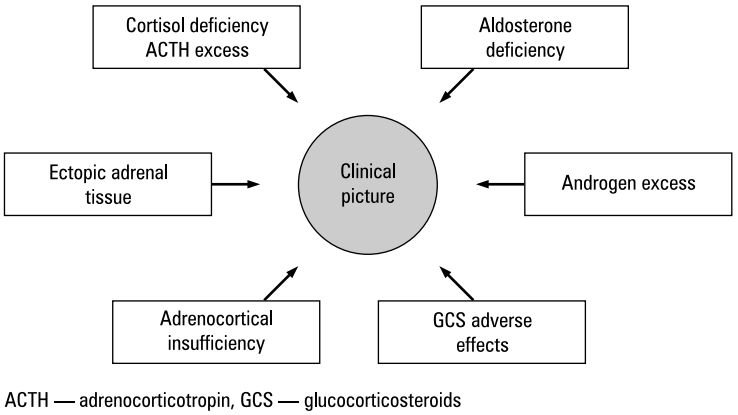

Figure 2. *Components of the clinical picture of CAH*

Rycina 2. *Składowe obrazu klinicznego CAH*

of: adrenocortical and adrenomedullary insufficiency, androgen excess and individual sensitivity to androgens, and the presence of ART and the adverse effects of the glucocorticosteroids (GCS) used for the treatment of this syndrome (Fig. 2).

Manifestations of adrenocortical and adrenomedullary insufficiency

Adrenocortical insufficiency is diagnosed in patients with classic CAH. Untreated or inadequately treated adult patients with CAH may present with the following symptoms: general malaise, easy fatigability, loss of appetite, and weight loss. Skin hyperpigmentation associated with high levels of ACTH may also be present in some patients. When adrenal crisis is imminent, abdominal pain, nausea, vomiting, diarrhoea, myalgia, low blood pressure, and postural hypotension additionally develop [7].

Patients with classic CAH also present with adrenomedullary insufficiency, which results from abnormal formation of the adrenal medulla in the prenatal period and from the disturbed synthesis of adrenomedullary hormones leading, beeing in either case consequence of cortisol deficiency. Patients with CAH have lower levels of plasma adrenaline, methoxy adrenaline, and urinary adrenaline compared to controls [8]. A reduced adrenaline response to brief, intense physical exertion has also been shown that fails to improve following administration of stress doses of GCS [9]. Adrenaline

deficiency combined with cortisol deficiency increases the risk of severe hypoglycaemia, especially in situations of increased requirement for adrenal cortex hormones [10]. Adrenaline deficiency that accompanies cortisol and aldosterone deficiency and excessive levels of progesterone, which has antimineralocorticoid effects, is also an additional risk factor for adrenal crisis in patients with classic CAH unresponsive to increased doses of GCS [1].

Reproductive system manifestations

The clinical picture in women with uncompensated adrenal dysfunction is dominated by manifestations of hyperandrogenism, such as hirsutism, acne, and menstrual disorders. In women with classic CAH insufficient development of the breasts is observed, which probably results from excessive exposure to androgens in antenatal life. About 40% of women with SW CAH and 20% of women with SV CAH suffer from fertility problems [11]. The causes of reduced fertility are complex:

— intrauterine exposure of the foetus to high concentrations of androgens may interfere with the development of the hypothalamic-pituitary-gonadal axis [12];
— high levels of progesterone, 17-OHP, and androgens adversely affect the dynamics of gonadotropin secretion and cause anovulation cycles [10];
— high levels of progesterone may also suppress the normal growth of endometrium and prevent the implantation of an embryo [13];
— frequent co-existence of PCOS and insulin resistance increases the risk of anovulation cycles;
— presence of ART in the ovaries may contribute to ovarian dysfunction [14];
— finally, fertility in women with classic CAH may be reduced as a result of sex life problems arising from abnormal anatomical structure of the external genitals or suboptimal outcomes of repair surgery. This group of women, more often than their healthy peers, report pain and bleeding during sexual intercourse.

The main manifestations of CAH in adult men are testicular adrenal rest tumour (ART) and infertility. The causes of male infertility include:

— ART (see below),
— LH suppression,
— co-existence of insulin resistance and metabolic syndrome.

LH suppression results from excessive aromatisation of androgens to estrogens, which leads to the suppression of gonadotropin release by the pituitary gland. Hypogonadotropic hypogonadism seen in these patients may also be associated with reduced testicular volume. It has, however, been shown that treatment with GCS may improve the quality of semen and fertility in this group of men with CAH [15, 16].

Therefore, men with CAH should have their semen tested at 3- to 5-year intervals, in addition to follow-up imaging studies of the testes.

Adrenal rest tumour

Adrenal rest tumour (ART) is found in the vicinity of the adrenal glands and along their embryonal pathway of descent. Its most common localisations include the coeliac plexus, broad ligament, testes (or ovaries in women), spermatic cord, kidneys, and other sites [14, 17]. The formation of ART is most frequently associated with the embryonic period of adrenomedullary incorporation into the adrenal cortex or with the presence of multiple adrenal anlagen [18]. ART is found in up to 50% of neonates and with time undergoes involution, so that its prevalence in the general population of adults is estimated at about 1%.

Testicular ART is present in at least a third of men with classic CAH, being more prevalent in patients with SW CAH. In one study, ultrasound scans revealed testicular ART in as many as 16 out of 17 young men [19]. ART are found already in early childhood below 10 years of age, even in adequately managed patients [20]. In poorly controlled patients with heterotopic localisation of adrenal cells, high ACTH levels may lead to testicular tumours. Clinical manifestations include testicular tenderness and enlargement. In the majority of cases these changes elude palpation. The diagnosis is made by ultrasonography, which reveals hypoechoic, usually bilateral foci that do not disturb the outlines of the testes [19]. MRI may be utilised in the diagnostic workup of testicular ART. The sensitivity of both imaging modalities in the diagnosis of ART is comparable [17].

ART in the testes may compress the seminiferous canaliculi and vessels, which may result in fibrosis of the parenchyma, potentially leading to abnormalities of spermatogenesis, Leydig cell dysfunction, and infertility. The discovery of focal changes in the testes may be a source of concern, as it may suggest the presence of a malignancy, such as malignant Leydig cell tumour. In the majority of cases, ART decreases in size as a result of GCS treatment, which is an important differentiating feature from Leydig cell tumour [21]. In equivocal cases a biopsy of the suspect changes may be considered although, despite the typical histological features for Leydig cell tumours (Reincke's crystals), the diagnosis may still be considerably difficult to make [22]. Hence, in patients in whom the ART fails to decrease in size following the administration of GSK, conservative surgery should be considered [23]. As in patients with oligospermia and pain, surgical treatment should be considered in cases of GSC failure. The outcomes of such treatment are good in terms of pain but uncertain in terms of improved quality of semen [24].

Table I. *BMD analysis in patients with CAH. Adapted from [10]*
Tabela I. *Analiza BMD u dorosłych chorych z CAH. Zmodyfikowano na podstawie [10]*

Study	Number of patients	Country	Results
Jaaskeleinen et al.	32 patients (30 with classic CAH, 16 women, aged 16–52 years) *v.* Finnish population	Finland	BMD (LS, FN) lower than in CG Negative correlation of BMD and GCS dose LA GCS — lower BMD
King et al.	26 female patients with classic CAH (21–71 years old) *v.* 9 CG	USA	Osteopaenia: 45% SW, 13% SV, 11% CG BMD (LS, WB) lower than in CG ($p < 0.05$) patients with osteopenia — reduced DHEA and DHEAS (mainly in postmenopausal women)
Sciannamblo et al.	30 patients with classic CAH (15 women, 16–29 years old) *v.* 138 CG	Italy	BMD WB lower than in CG ($p < 0.03$) Bone fraction ALP and C-telopeptide higher in CAH ($p < 0.04$) No correlation between BMD or bone turnover markers and the dose of GCS
Falhammar et al.	61 females (55 with classic CAH, 18–63 years old) *v.* 61 CG	Sweden	BMD (LS, FN, WB) lower than in CG ($p < 0.001$) < 30 years osteopaenia 48% *v.* 12% CG > 30 years osteopaenia 73% *v.* 21% CG Osteoporotic fractures more often in CAH ($p = 0.058$)

LS — lumbar spine, FN — femoral neck, CG — control group, WB — whole body

Manifestations of non-classic congenital adrenal hyperplasia

Late-onset NC CAH accounts for about 1–2% of hyperandrogenism syndromes in Caucasians [25, 26]. The most common manifestations in adult women include: hirsutism, oligomenorrhoea, acne, infertility, frontal alopecia, and, rarely, primary amenorrhoea or manifestations of virilisation (male pattern hair growth, clitoromegaly, deepening of the voice). Fertility disorders affect about 13% of women with NC CAH [27]. The causes of infertility are complex and similar to those in the classic forms of CAH. In some women the course of the disease is asymptomatic, as confirmed in family studies of patients diagnosed with NC CAH.

Although the incidence of NC CAH in men and women is the same, few publications discuss the former, mainly because of the asymptomatic course of the disease in this sex. In most men with NC CAH the function of Leydig cells is preserved and spermatogenesis is normal, although some do exhibit ART and fertility disorders [6].

Adrenal tumours

Focal changes in the adrenal glands, both unilateral and bilateral, are definitely more prevalent in patients with CAH, in both the classic and non-classic forms [28]. The higher prevalence is also observed among heterozygous patients (*CYP21A2* gene mutation carriers) compared to the healthy population [28]. Adrenal tumours in CAH patients may decrease in size following treatment with GCS. There are only isolated reports of adrenocortical carcinoma in patients with CAH [29, 30]. Patients suffering from CAH should therefore be examined for adrenal tumours, and patients with adrenal tumours should be examined for CAH.

Height and bone mineral density

Adult patients with classic CAH are shorter than average individuals in the general population by 1.4 SD (10 cm) [31]. This results from the earlier exposure to androgens and the accelerated growth rate in early childhood coupled with premature epiphyseal closure in the long bones on the one hand and from the suppressive effects of excessive GSC doses on the secretion of growth hormone on the other. Short stature may be a consequence of hyperandrogenism and transient hypercortisolaemia in childhood.

Long-term GCS treatment is a known risk factor for reduced bone mineral density (BMD). While studies in children have found no BMD decreases, studies in adults have demonstrated significantly lower BMD in patients with CAH versus controls [32–36] (Table I). The group at highest risk of low BMD are patients with SW CAH, who are managed with the highest doses of GCS.

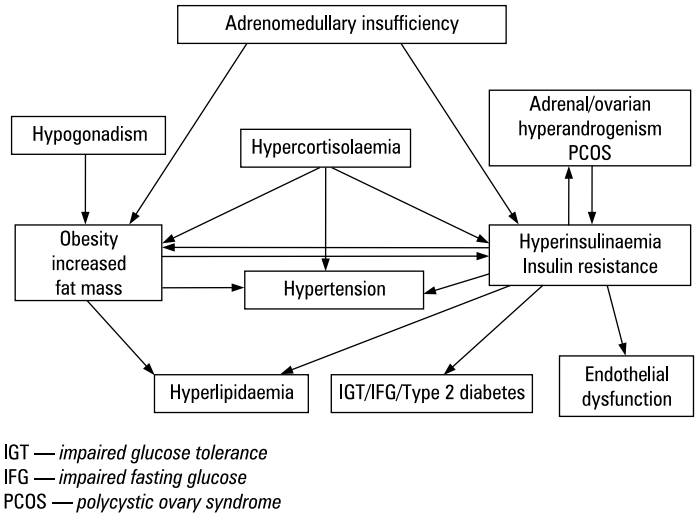

Figure 3. *Metabolic associations in patients with classic CAH. Adapted from [73]*
Rycina 3. *Zależności metaboliczne u chorych z klasyczną formą CAH. Zmodyfikowano na podstawie [73]*

It has also been shown that lower BMD values are found in patients managed with longer-acting GCS compared with those managed with hydrocortisone [34]. Moreover, osteopaenic patients have exhibited reduced levels of androgens: dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS), which was particularly the case with postmenopausal women managed with long-acting GCS [35]. A Swedish study by Falhammar et al. attracted particular interest, as it followed up a subgroup of patients over 30 years of age. Signs of osteopaenia were found in 73% of women with classic CAH versus 21% of control patients. The study was also the first study to have pointed to the increased tendency for osteoporotic fractures (spine, femoral neck, and wrist fractures) in patients managed with GCS [36].

Indications for the determination of bone turnover markers in patients with CAH have not been defined.

To summarise the findings of the above studies, several causes of reduced BMD in adult patients with CAH may be identified:

— long-term treatment with GCS;
— the use of longer-acting GCS exhibiting a greater ACTH-suppressing potential and hence a greater androgen-suppressing potential;
— the use of higher doses of GCS;
— co-existence of other risk factors for osteoporosis, *e.g.* hypogonadism.

These findings point to the necessity of constant monitoring of the bones and osteoporosis prevention. The use of the lowest possible doses of GCS, avoidance of long-acting GCS in peri- and postmenopausal women, and detailed monitoring of other factors contributing to the development of osteoporosis should be the first step towards the prevention of bone mass loss in patients with CAH. A diet high in calcium and vitamin D, calcium and vitamin D supplementation, and appropriate physical activity are further basic recommendations for these patients. A periodic bone densitometry in adults with CAH is also recommended.

Metabolic syndrome

Classic CAH is a considerable risk factor for metabolic syndrome, as patients with these variants of the disease exhibit increased body fat, increased incidence of overweight/obesity, higher insulin levels, and insulin resistance [37, 38].

The main causes of metabolic abnormalities in patients with CAH are periodic hypercortisolaemia (which cannot be avoided during GCS treatment), insufficiency of the adrenal medulla, and hyperandrogenism (Fig. 3) [8].

Following a single oral dose of hydrocortisone, the peak serum concentration is achieved within 1–2 hours with the drug having been completely cleared from the serum within 5–6 hours [39]. Patients with CAH are therefore at risk of constant or periodic hypocortisolaemia coupled with stimulation of the adrenal cortex by ACTH, or of transient hypercortisolaemia.

The adrenomedullary insufficiency occurring in patients with classic CAH carries with it some important metabolic implications:

— adrenaline deficiency is one of the factors promoting hyperinsulinaemia and insulin resistance as a result of the absence of inhibition receptor β3-mediated catecholamine effects on insulin secretion [40];
— in the same mechanism, adrenaline deficiency promotes hyperleptinaemia [40];

— adrenaline deficiency promotes obesity. Activation of the sympathetic nervous system increases lipolysis, reduces storage of triglyceride-rich lipoproteins in the adipose tissue, and increases thermogenesis in the brown adipose tissue. All this depletes the fat stores. In adrenaline deficiency, thermogenesis and lipolysis are impaired contributing to increased body fat [40].

Hyperandrogenism is another factor that decreases insulin sensitivity and leads to hyperinsulinaemia most likely resulting from the stimulation of secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1).

Hyperinsulinaemia and insulin resistance coupled with obesity and periodic hypercortisolaemia may all promote the development of hypertension, dyslipidaemia, abnormalities of carbohydrate metabolism, and direct endothelial injury, increasing cardiovascular risk in patients with CAH. One study showed an absence of the nocturnal dip in systolic blood pressure in 84% of patients with classic CAH, which is considered a significant cardiovascular risk factor [41]. Nineteen patients with classic CAH and a mean age of 28.5 years exhibited, in addition to reduced insulin sensitivity, an increased intima-media thickness (IMT) versus controls, which is an early indicator of atherosclerosis and another important cardiovascular risk factor [42].

Normalisation of blood pressure and modification of metabolic abnormalities are known to slow down the progression of atherosclerotic changes significantly. Patients with classic CAH should therefore be carefully monitored for metabolic syndrome elements. Early lifestyle intervention, consisting mainly of appropriate diet and exercise, may reduce cardiovascular risk in this group of patients.

Psychosocial problems and quality of life

A recent study evaluating quality of life in patients with CAH carried out at 17 centres in the UK followed up 203 patients (65 men and 138 women aged 18–69 years) and demonstrated, in contrast to previous observations, that the quality of life in patients with CAH was significantly reduced compared to the quality of life in patients with congestive heart failure and patients on haemodialysis [43].

Psychosocial problems in women with CAH are an important issue. They result from the effects of androgens on the CNS functions (in the pre- and postnatal period) on the one hand and from the somatic consequences of hyperandrogenisation on the other [44]. Female patients with CAH are more frequently lonely, are less sexually active, and have an inferior body image and an inferior perception of themselves in the group [45]. Homosexual and bisexual behaviour is also more prevalent among women with classic and non-classic CAH.

When cognitive function was evaluated in patients with CAH their IQ values were not found to differ significantly from those in the control group [46]. Only patients with SW CAH who underwent adrenal crises and were exposed to hypoglycaemia or electrolyte imbalance in their childhood may present lower IQ values [47].

Diagnostic evaluation of congenital adrenal hyperplasia

Diagnostic evaluation of the classic forms of congenital adrenal hyperplasia

The classic form of CAH (SW CAH), due to its clinical signs and symptoms of salt loss in both sexes (additionally accompanied in girls by abnormal external genitalia), is detected, in the majority of cases, in the neonatal period. On the other hand, SV CAH in boys and in girls with a mild clitoromegaly may not be diagnosed until early childhood when signs of precocious puberty develop. Mild clinical forms of SV CAH are sometimes not diagnosed until adulthood.

The laboratory diagnosis of classic CAH is based on the following:

— determination of serum levels of 17-OHP,
— ACTH stimulation test,
— urinary steroid profile by gas chromatography/mass spectrometry (GC-MS),
— testing for *CYP21A2* gene mutations.

The screening test for CAH due to 21-hydroxylase deficiency involves the determination of 17-OHP in a blood drop collected on a filter paper 3–5 days after birth.

Neonatal screening in many European countries and many states in the US enables early detection of CAH due to 21-hydroxylase deficiency.

In most patients with SW CAH or SV CAH, the serum levels of 17-OHP exceed 100 ng/ml (with the normal values equalling < 1–2 ng/ml, depending on age, sex, and test kit) [48].

Because of the risk of false positive results (preterm babies, birth weight below 2500 g, distressed neonates) all the elevated 17-OHP results require verification by the methods mentioned above (bullets 2–4) [49].

Basing the diagnosis merely on 17-OHP determinations in the serum may also be the reason for misdiagnosing 21-hydroxylase deficiency, as it should be borne in mind that elevated levels of 17-OHP are also found in other abnormalities of steroidogenesis, such as:

— CAH due to 11β-hydroxylase deficiency,
— CAH due to type 2 3β-hydroxysteroid dehydrogenase (3β-HSD2) deficiency,
— 17,20-lyase deficiency with normal cortisol levels,

— reduced sensitivity of the glucocorticosteroid receptor,
— CAH due to the deficiency of P450 oxidoreductase, which is a cofactor of 21-hydroxylase, 17α-hydroxylase, and aromatase.

In addition, elevated 17-OHP levels are also observed in preterm babies and newborns with birth weight below 2500 g. This results from cross-reactions between the antibodies used in the 17-OHP assays and steroids of the still very active foetal layer of the adrenal cortex.

Neonates born at term during distress (stress stimulation of the adrenal cortex by ACTH) also secrete increased amounts of 17-OHP [50].

The ACTH stimulation test measuring 17-OHP following the administration of synthetic adrenocorticotropic hormone is used in diagnostically ambiguous cases and for the differentiation between classic and non-classic CAH [50, 51]. Tetracosactide (Synacthen) at a dose of 250 μg is given via intramuscular injection, and serum 17-OHP concentrations are determined at baseline and at 30 and 60 minutes after dosing, although some centres prefer to determine 17-OHP at two time points: at baseline and at 60 minutes [17]. The post-stimulation levels of 17-OHP are generally highest in SW CAH (300–1000 ng/ml), intermediate in SV CAH (100–300 ng/ml), and lowest in NC CAH (15–100 ng/ml).

Urine steroid profiling by GC/MS enables a precise assessment of steroidogenesis abnormalities. A single portion of urine suffices to establish the diagnosis of CAH due to 21-hydroxylase, 11β-hydroxylase, 17α-hydroxylase, or 3β-HSD deficiency. The diagnosis of other steroidogenesis disorders associated with the signs and symptoms similar to CAH due to 21-hydroxylase deficiency requires a 24-hour urine collection [50, 52].

Although 21-deoxycortisol is the marker typical of 21-hydroxylase deficiency of purely adrenal origin, no commercial assays for determining its serum levels are available. Pregnanetriolone, determined in the steroid profile by GC/MS, is the metabolite of this steroid.

Patients with SW CAH have reduced blood levels of aldosterone and 11-deoxycorticosterone and elevated plasma renin activity (PRA), hypernatraemia, hyperkalaemia, and metabolic acidosis [49].

Recent studies have shown that a mild aldosterone deficiency is also present in SV CAH and NC CAH, although it is not accompanied by biochemical signs of salt wasting. These patients have an abnormal (reduced) ratio of serum aldosterone to PRA. The increased PRA stimulates the mildly disrupted aldosterone synthesis to a level that ensures normal sodium concentrations, which is why the aldosterone–PRA ratio may be used to assess aldosterone synthesis in patients with various forms of CAH due to 21-hydroxylase deficiency [53].

Genetic testing with the assessment for *CYP21A2* mutation enables diagnosis in 90–95% of patients.

Diagnostic evaluation of non-classic congenital adrenal hyperplasia

The diagnostic evaluation of NC CAH involves:
— Determination of serum 17-OHP,
— ACTH stimulation test,
— Urinary steroid profiling,
— Genetic testing for *CYP21A2* mutations.

The diagnosis of NC CAH is most commonly based on the determination of baseline 17-OHP levels and the ACTH stimulation test. Unfortunately, the reference values of 17-OHP prior to and following stimulation are not unequivocally established. Due to the circadian rhythm of 17-OHP secretion (parallel to that of cortisol) and its adrenal (10%) and gonadal (90%) origin, it is recommended that the diagnostic evaluation in menstruating women should be performed in the follicular phase (between days 7 and 9 of the cycle) in the early morning hours. The following interpretation of results is currently proposed [54, 55]:
— 17-OHP levels in the follicular phase below 2.0 ng/ml (or below 1.7 ng/ml, as preferred by other authors) rules out the diagnosis of NC CAH with a high likelihood;
— 17-OHP levels between 1.7 and 2.0 ng/ml are an indication for the ACTH stimulation test;
— 17-OHP levels exceeding 4.0 ng/ml are highly suggestive of NC CAH and an indication for the ACTH stimulation test;
— 17-OHP levels exceeding 10.0 ng/ml in the follicular phase confirm the diagnosis of CAH.

The ACTH stimulation test is frequently decisive in the diagnostics of NC CAH. The 17-OHP concentrations following ACTH stimulation that are typical of NC CAH are most commonly in the range of 15–100 ng/ml [51]. Most authors consider 17-OHP levels ≥ 10 ng/ml the lowest cutoff value for the diagnosis of NC CAH [55] although asymptomatic carriers (heterozygotes) may also fall between the values of 10 and 15 ng/ml. As in the classic forms of CAH, urinary steroid profiling by GC/MS (where metabolites of 17-OHP, 21-deoxycortisol, cortisol, and androstenedione are simultaneously determined) and genetic testing for *CYP21A2* mutations may prove helpful in establishing the diagnosis.

Molecular studies have identified a separate genotype of NC CAH compared to the classic forms. Patients may carry two mild mutations on both alleles (most commonly V281L and P30L) or have combined heterozygotes with a mild mutation on one allele and a severe mutation on the other, typical of SW CAH and SV CAH [6].

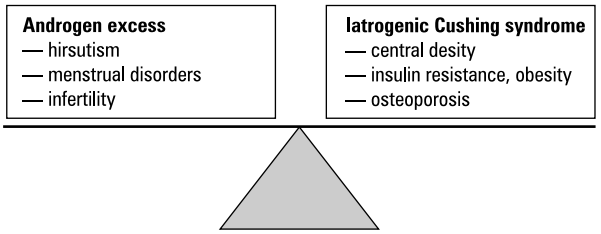

Figure 4. *Difficulties in the management of CAH patients [10]*
Rycina 4. *Trudności w leczeniu CAH. Zmodyfikowano na podstawie [10]*

Female patients with NC CAH have an increased 24-hour excretion of the aldosterone metabolite tetrahydroaldosterone (THAldo), which — similarly to patients with SV CAH — reflects the stimulation of aldosterone formation by renin to compensate for the mild aldosterone deficiency [56].

Management of congenital adrenal hyperplasia

The management of CAH depends on the age of onset, sex, and the severity of enzyme deficiency. The principal goals of treatment in patients with classic CAH is to improve the quality of life, to correct glucocorticosteroid and mineralocorticosteroid deficiency and to reduce the signs of hyperandrogenism in girls/women. Treatment often improves fertility in both sexes. There is no consensus as to the management of CAH that would comply with the principles of evidence-based medicine (EBM). In addition, the widely varied clinical picture of patients with CAH compels an individual approach to patient management.

Glucocorticosteroids

Patients with the classic forms of CAH, both SW CAH and SV CAH, require treatment with glucocorticosteroids and, in the case of SW CAH, with fludrocortisone.

Glucocorticosteroid treatment of patients with CAH is very difficult. The substitutive doses of GCS are sufficient to manage adrenocortical insufficiency but in the majority of cases fail to provide sufficient suppression of ACTH secretion or to prevent hyperandrogenism. On the other hand, supraphysiologic doses of GCS effectively suppress ACTH secretion and reduce androgen levels but are associated with adverse effects. Finding "the golden mean" for each particular patient is therefore quite a challenging task (Fig. 4).

While in children hydrocortisone 3–4 times daily is the basic GCS, in adults the administration of longer-acting GCS given once or twice daily is more commonly recommended [10]. The GCSs used in adults include: prednisone 5.0–7.5 mg/day, prednisolone 5–10 mg/day, dexamethasone (DXM) 0.25–0.50 mg/day, hydrocortisone 15–45 mg/day, or a combination of several GCSs. Fludrocortisone in adults is usually used at a dose of 50–100–200 μg/day. A reduction in the sensitivity to sodium loss is observed with age, so that salt replenishment is no longer required in adults as it is in children and treatment with increasingly lower doses of fludrocortisone is possible [1]. Unfortunately, there is no single dose equivalent for specific glucocorticosteroids. The most commonly cited one is 1 mg of dexamethasone = 16 mg of prednisone = 80 mg of hydrocortisone [57]. According to other sources, the equipotent doses are 1 mg of dexamethasone = 7 mg of prednisone = 27 mg of hydrocortisone [58]. Individual sensitivity to GCS (especially DXM) is very important here. The dose should always be selected on an individual basis, carefully observing the patient, monitoring for side effects, and evaluating endocrine parameters (see below).

No randomised clinical studies have been performed to assess the various glucocorticosteroid formulations and the various glucocorticosteroid regimens. Preferences for the individual formulations vary between centres. Among the patients managed at Middlesex Hospital in London, patients with SW CAH have most commonly received prednisolone (53%), followed by hydrocortisone (37%), dexamethasone (4%), and combinations of various GCSs (5%). All patients have also received fludrocortisone at doses of 50–400 μg. Patients with SV CAH have received hydrocortisone (42%), prednisolone (31%), dexamethasone (3%), and combinations of various GCSs (12%), while 12% remained without treatment. In this group of patients 38% have also received fludrocortisone [13]. In most adult cases, in order to prevent the morning ACTH and 17-OHP peaks, the only or the highest GCS dose is used in the evening.

Treatment in NC CAH is only indicated in symptomatic cases. Glucocorticoid treatment in women may be considered if hyperandrogenism, menstruation disorders, or infertility is present. Irregular menses and acne usually subside within about 3 months of treatment with GCS, while hirsutism does not resolve until about 30 months of treatment [6]. This is why female patients with NC CAH receive antiandrogens in addition to or instead of GCS, and oral contraceptives.

In order to induce ovulation, if GCS fail, clomifene citrate is most commonly used [11].

Adult men with NC CAH require GCS treatment only if ART and/or oligospermia are present.

Although primary adrenocortical insufficiency is not observed in patients with NC CAH, patients on long-term glucocorticoid treatment may develop secondary adrenocortical insufficiency. Hence, in distressing situations (infection, surgery), they should be receiving appropriately increased doses of GCS.

In women with CAH, both classic and non-classic, who are planning to become pregnant, DXM should not be used (see below).

Bilateral adrenalectomy

Bilateral adrenalectomy is a rarely used procedure with limited indications. The principal indication is drug-resistant hyperandrogenism, in which case adrenalectomy allows the use of lower doses of GCS aimed only at replenishing the hormone deficiency. A five-year study investigated 18 patients with CAH who had undergone bilateral adrenalectomy. Hyperandrogenism resolved, but the patients still required relatively high doses of GSC (equivalent to hydrocortisone 11 mg/m^2/day) to prevent hyperpigmentation and ART [59]. Another potential indication may be to maintain high progesterone levels in the follicular phase that are not suppressed by GCS treatment. This leads to ovulation abnormalities on the one hand and to endometrial atrophy and implantation abnormalities on the other. Bilateral adrenalectomy performed in two female patients resulted in normalisation of progesterone levels and becoming pregnant [13]. However, such treatment should be limited to special situations due to the risk of the surgery itself and the high changes of development of ART.

Reconstructive treatment

In girls with classic CAH, plastic surgery of the external genitals is an equally important element of management as drug treatment. The methods of reconstructive surgery in many female patients qualified for the treatment vary with the country. The expertise of centres specialising in the treatment of this type of anomalies enables constant progress and improvement of surgical techniques. For several years now, surgery has been indicated in female neonates with CAH [49]. It is less and less common that plastic surgery of the genitals needs to be repeated in adult age, which only 10–15 years ago was commonplace [60].

The following are considered the criteria of successful reconstructive surgery [2]:

— urinary continence,
— free outflow of menstrual blood,
— possibility of easily inserting safety tampons,
— possibility of full vaginal penetration during sexual intercourse,
— possibility of achieving expected sexual satisfaction,
— good cosmetic effect.

Treatment of hyperandrogenism syndrome

Some women with classic and non-classic CAH require treatment with oral contraceptives with the aim of regulating the menstrual cycle and preventing changes in the ovaries typical of PCOS. Similarly, in cases of severe signs of hyperandrogenisation, such as hirsutism and acne, oral contraceptives and antiandrogens (cyproterone acetate, spironolactone) may be helpful [2]. The effectiveness of both therapies, especially in terms of managing hirsutism, is considered superior to GCS [61]. Oral contraceptives increase the synthesis of sex hormone binding globulin (SHBG) in the liver, increasing its blood levels, reducing free androgen levels, blocking androgen receptors, and suppressing both ovarian and adrenal androgens through effects on ACTH, which is why, in addition to regulating the menstrual cycle, they are also employed in the treatment of hirsutism in female patients with CAH.

Flutamide is also used in the treatment of severe hyperandrogenisation (androgen receptor blocking) as well as finasteride (inhibition of 5α-reductase) [62, 63].

Novel treatments

Current studies investigating novel treatments for adults with CAH focus on the use of CRH receptor antagonists and gene therapy.

The CRH receptor antagonist antalarmin is a CRH-1 receptor antagonist. By binding with the target receptor, antalarmin blocks the binding of the natural CRH ligand, thereby suppressing ACTH secretion in another mechanism than GCS does [64]. Preliminary results of animal studies are promising, but the drug is still in the investigative phase.

Gene therapy as a potential method of radical treatment for CAH patients is still in the experimental phase. It is difficult to tell when the method will be found useful in clinical practice.

Treatment during pregnancy

Dexamethasone is a steroid that is not a substrate for placental 11β-hydroxysteroid dehydrogenase 2 (11βHSD2), thanks to which it passes through the placenta to the foetus. The only indication for using dexamethasone during pregnancy is prenatal management of a female foetus at risk of classic CAH. The criteria to be met before considering prenatal treatment in carriers (heterozygotes) are as follows [2, 49]:

— presence of siblings with a mutation causing classic CAH confirmed by DNA testing,
— determination of the parents' (heterozygotes') genotypes in terms of *CYP21A2* mutations,
— possibility of rapid DNA analysis for *CYP21A2* mutations in the foetus,
— possibility of initiating treatment less than 9 weeks since the last menstrual period,
— parents' decision to keep the pregnancy,
— compliance on the part of the parents.

Dexamethasone must be initiated at 6 weeks of gestation (preferably right after the pregnancy has been confirmed) because its aim is to eliminate virilisation of

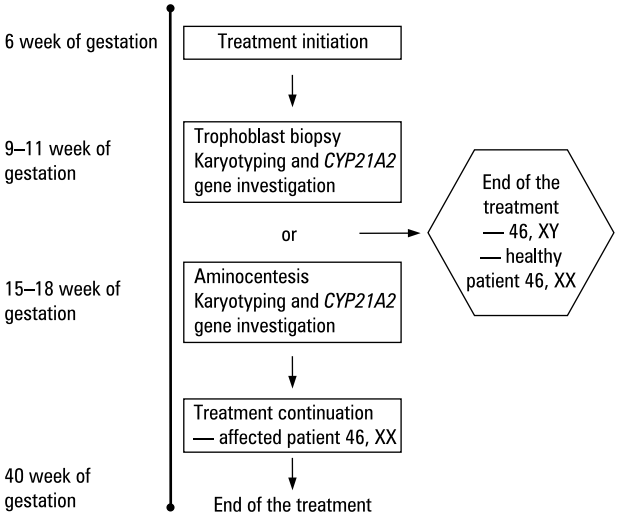

Figure 5. *Diagram of prenatal management of CAH with dexamethasone*

Rycina 5. *Schemat leczenia prenatalnego CAH deksametazonem*

the genitals of the female foetus. The genetic evaluation of the material obtained during trophoblast biopsy and amniocentesis is not possible before 9–11 and 15–18 weeks of gestation, respectively [65–67], which is why during the first phase of treatment or before the genetic testing results have come back some of the foetuses receive treatment unnecessarily. In spite of the confirmed efficacy of prenatal management of CAH in terms of achieving normal structure of the external genitals in girls, there is no consensus as to the safety of DXM for both the mother and the child [1, 49, 65, 68, 69]. Such treatment should therefore be regarded as a medical experiment, as its remote consequences are presently unknown. The unnecessary treatment of most foetuses (female foetuses without *CYP21A2* mutations, male foetuses with or without *CYP21A2* mutations) is an ethical problem. Treatment may be conducted in specialised centres, after approval of the relevant ethics committees has been granted and after the mother to be given dexamethasone has signed a written informed consent form. Specialist maternal monitoring, followed by long-term monitoring of the babies is necessary during the treatment. A diagram of prenatal management is presented in Figure 5.

During pregnancy, women with CAH should receive a GCS that does not penetrate the placenta (hydrocortisone, prednisone, prednisolone). Hydrocortisone is the preferred drug in most centres. DXM may only be used in prenatal therapy [49]. The dosage of GCS and monitoring of treatment is the same as in non-pregnant women, although some authors prefer to monitor the levels of testosterone, which should not exceed 2 ng/ml in this period. Elevated androgen levels in pregnant women with CAH do not result in virilisation of healthy female foetuses because of the activity of placental aromatase, high SHBG levels, and the anti-androgenic effects of high progesterone levels [1]. The baby should be delivered at a reference centre, with elective caesarean section being the only delivery option in women with a history of plastic surgery of the genitals [2]. In the perinatal period the mother should receive increased doses of GCS, as in distressing situations.

The use of GCS and mineralocorticoids by mothers with CAH is not a contraindication for breastfeeding, although both GCS and MCS are excreted to human milk. The levels of DXM and fludrocortisone in human milk have not been established.

Women with NC CAH who did not receive GCS before pregnancy do not require treatment with GCS during pregnancy. Women who did receive GCS after becoming pregnant require continuation of treatment with a GCS that does not penetrate the placenta, at substitutive doses, according to the generally accepted principles of management in secondary adrenocortical insufficiency.

Genetic testing and genetic counselling

The development of molecular diagnostics in CAH and the availability of prenatal treatment have made it necessary to provide the patients — potential parents — with as much information about the risk of CAH in their offspring and treatment options as possible. An evaluation of the risk of giving birth to a girl with classic CAH in several clinical situations is presented in Table II.

Monitoring of treatment

While the principal goal of paediatric care is to monitor the correct physical development and the correct sexual maturation of the patients, the management in adults should be focused on avoiding complications of long-term steroid treatment. The management strategy should take into consideration the selection of the lowest effective dose of GCS, as assessed by clinical and biochemical parameters.

No GCS treatment monitoring standards for adult patients with CAH due to 21-hydroxylase deficiency have been established so far.

The clinical parameters that need to be monitored include: the presence of Cushingoid manifestations; body weight and body fat; waist circumference; blood pressure; bone mineral density; and periodic ultrasound scan of the testicles and examination of the semen in men. The principal biochemical parameters used to monitor GCS treatment include 17-OHP, androstenedione, and testosterone.

Table II. *Assessment of the risk of giving birth to a girl with classic CAH in selected clinical situations*
Tabela II. *Ocena ryzyka urodzenia dziewczynki z klasyczną formą CAH w wybranych sytuacjach klinicznych*

Clinical situation	Chances of giving birth to a girl with classic CAH
One child with classic CAH	1/8
One partner with classic CAH, unknown genetic status of the other partner	0.4% or 1/250 [1 parent 2 classic alleles] × [1.6% carriers with classic mutation] × [1/2 chance that the carrier will pass on the allele to the child] × [1/2 chance that the foetus is female]
One partner with non-classic CAH, unknown genetic status of the other partner (50% compound heterozygotes)	0.1% or 1/1000 [50% carriers with classic mutation] × [1.6% carriers with classic mutation in the general population] × [1/4 chance that both classic alleles will be passed onto the offspring] × [1/2 chance that the foetus is female]

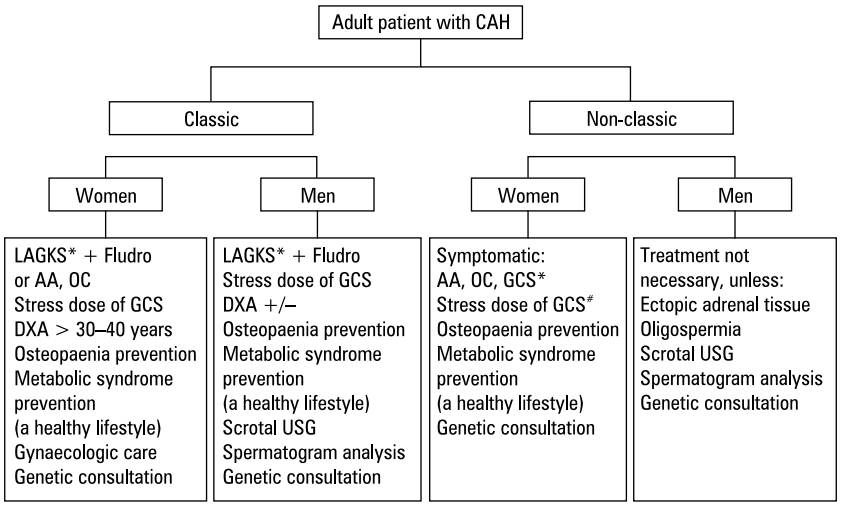

Figure 6. *Management of patients with classic and non-classic CAH. Adapted from [10].*
Rycina 6. *Schemat postępowania u chorych z klasyczną i nieklasyczną postacią CAH. Zmodyfikowano na podstawie [10]*
**Long-acting GCS should not be the drugs of choice in elderly patients. #Stress dose of GCS in cases of long-term GCS use*

Suppression of 17-OHP to normal limits for healthy individuals should be avoided because it would involve the use of GCS doses resulting in adverse effects. An optimal dose of GCS should maintain androgens within normal ranges and 17-OHP (within the range of 4–12 ng/ml) [70]. However, achieving target 17-OHP values should be individualised. In young women trying to become pregnant, 17-OHP levels should not exceed 8–10 ng/ml, while the concentration of the hormone in adult men without signs of testicular ART should be kept below 25 ng/ml [10].

Monitoring of treatment with mineralocorticosteroids

PRA is the basic biochemical parameter used in the monitoring of fludrocortisone treatment. As there is no consensus as to the conditions in which PRA should be tested, determination of the parameter after 2 hours of remaining in the vertical position (sitting, standing, or while walking) seems the most appropriate. It is recommended that the screening PRA values should be within normal or slightly above normal range (up to 2 times the upper limit of norm) [13]. Excessive PRA suppression is suggestive of mineralocorticosteroid overdose. Excessively high values of PRA correlate with elevated angiotensin II, which is known to stimulate the initial stages of adrenal steroidogenesis on the one hand and to be a cardiovascular risk factor on the other [71, 72]. Sodium and potassium are two other biochemical parameters that reflect water and electrolyte balance in patients on mineralocorticosteroids, although these parameters are less reliable in older children and adults. The clinical parameters that require monitoring include oedema and blood pressure.

The proposed management algorithm for adult patients with CAH is presented in Figure 6.

Summary

While the goals and principles of management in children have been well described in the past fifty years, the management of adults with CAH is mostly based on experiences gained in small and relatively young patient groups. EBM-based standards are still lacking. However, preliminary observations allow the identification of the tasks to be addressed in the care for an adult patient with CAH:

— to establish the treatment goals,
— to establish further management with GCS,
— to minimise and monitor for adverse effects of GCS,
— to improve sexual function,
— to improve fertility,
— to provide psychological support,
— to prevent osteopaenia,
— to prevent metabolic syndrome and limit cardiovascular risk.

These tasks should be carried out at reference centres in collaboration with a number of specialists, including endocrinologists, gynaecologists, urologists, dieticians, sexologists, geneticists, and psychologists, which should lead to optimal outcomes in adult patients with CAH.

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