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Review

Non-Classic Congenital Adrenal Hyperplasia in Childhood: A Review

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Abstract: Congenital adrenal hyperplasia (CAH) is a heterogeneous group of autosomal recessive disorders due to defects in adrenal steroid biosynthesis. In about 90% of patients, CAH is caused by pathogenetic variants in *CYP21A2* gene, impairing the function of 21-hydroxylase (21-OH) enzyme. CAH can present as classical form (simple virilizing or salt wasting) or as non-classical form (NC-CAH). NC-CAH is due to pathogenetic variants in the *CYP21A2* gene that result in 20–70% residual activity of 21-hydroxylase. Early diagnosis may be missed, mainly in childhood, jeopardizing long-term outcome. This paper will review some information on clinical findings, symptoms, diagnostic approaches, and treatments of NC-CAH in childhood, allowing better management and long-term outcome.

Keywords: non-classical congenital adrenal hyperplasia; 21-hydroxylase; *CYP21A2* gene; diagnosis; hydrocortisone; treatment

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1. Introduction

The term "congenital adrenal hyperplasia" (CAH) indicates a family of autosomal recessive disorders due to mutations in genes encoding the enzymes involved in the biosynthesis adrenal steroid hormones. Genetic variants in the *CYP21A2* gene (MIM# 613815) are found in most of the patients with CAH (>90%) [1]. The *CYP21A2* gene encodes the adrenal steroid 21-hydroxylase enzyme (P450c21) that converts 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and progesterone to deoxycorticosterone, respective precursors for cortisol and aldosterone. The cortisol synthetic block leads to corticotropin (ACTH) stimulation of the adrenal cortex, with accumulation of cortisol precursors, that are diverted to sex hormone biosynthesis (Figure 1) [2].

CAH is clinically classified as classic form (C-CAH) with salt wasting (SW) or simple virilizing (SV) phenotypes, and non-classic form (NC-CAH) [1,2]. These clinical presentations are related to different residual degrees of 21-hydroxylase (21-OH) enzyme activity (Table 1) [3,4]. Reduced 21-OH enzyme activity leads to cortisol deficiency and in turn stimulation of the pituitary-adrenal axis with increased ACTH secretion and abnormal production of intermediated metabolites, that are shifted toward androgen biosynthesis (Figure 1) [1,3–5].

Classic CAH is usually diagnosed at birth or in the first months of life due to the occurrence of ambiguous genitalia in girls (in the case of SW and SV phenotypes) and peripheral isosexual precocious puberty in boys (in the case of SV form) [1]. In addition, life threatening salt loosing crisis may occur, when 21-OH activity is 0–5%, impairing production of both cortisol and aldosterone [1,5]. The clinical manifestations of NC-CAH show a later onset and variable clinical features (see below). They are mainly related to mild androgen excess, and the phenotype may progressively worsen with age [2,6].

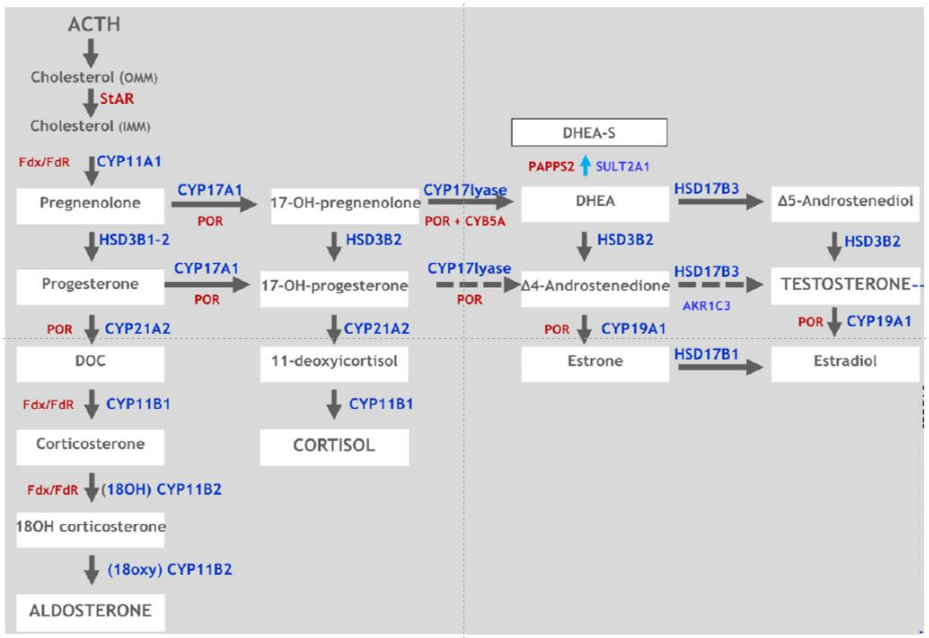

Figure 1. Adrenal steroidogenesis: schematic overview of classic biosynthetic pathway. (The backdoor pathway is not shown).

Table 1. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Phenotypes, gene defects and related residual enzyme activity [3,4].

CAH Phenotype	Genetic Status of *CYP21A2* Gene Variants		21-OH Residual Activity, %
	Homozygous	Heterozygous	
Salt wasting	Null/Null	A/Null or A/A	0–1
Simple virilizing	B/B	B/A or B/Null	1–5
Non-classic	C/C	C/B or C/A or C/Null	15–60
Carriers	Null or A or B or C		>60 *

Null = deletions/large gene conversions; A = severe gene variants; B = medium severity of genetic variants; C = mild genetic variants. * Carries may show some mild clinical manifestations according to the severity of *CYP21A2* gene variant.

Old studies reported a 1:700 to 1:1.000 prevalence of NC-CAH in the Caucasian population; higher prevalence has been reported in some ethnic groups [Ashkenazi Jews (1:27), Hispanics (1:53); Slavic (1:62); Italians (1:300)]. Recent data by *CYP21A2* genotyping suggest a prevalence of NC-CAH in the Caucasian population (1:200) higher than that indicated in old epidemiologic studies by assessment of 17-hydroxyprogesterone (17-OHP) levels or HLA linkage analysis [7]. Hannah-Shmouni et al. [7] stated that NC-CAH is likely common across ethnicities at least in US population; they also suggested that large differences between Caucasian and Ashkenazi people may be not operative [7].

NC-CAH is more frequently diagnosed in adult females [2,6], as well as in girls than in boys (Table 2). This is an unexpected asymmetry for a recessive autosomal disease, but an ascertainment bias may have a role in the discrepancy between the diagnostic rate in the two sexes since symptoms of hyperandrogenism (see below) are more alarming in the female sex.

Table 2. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Mean age at diagnosis in children and female/male sex ratio in recent large pediatric series.

Authors	Total Series, *n*	Age at Diagnosis, Years	Females, *n* (%)	Males, *n* (%)	Ratio
Eyal et al. [8]	122	11.3 ± 7.7	99 (81%)	23 (19)	4.3/1.0
Livadas et al. [9]	107	F 0.6–6.8 * M 2.0–8.9 *	94 (88)	13 (12)	7.2/1.0
Savas-Erdeve et al. [10]	258	9.8 ± 4.3	229 (89)	29 (11)	7.9/1.0
Dörr et al. [11]	134	7.1 ± 4.4	105 (78)	29 (22)	3.6/1.0
Wasniewska et al. [12]	192	7.4 ± 3.7	140 (73)	52 (27)	2.6/1.0
De Vries et al. [13]	114	7.9 ± 4.2	92 (81)	22 (19)	4.2/1.0

F = females; M = males; * age range at diagnosis.

The p.(Val282Leu) pathogenic variant on exon 7 of the *CYP21A2* gene is the main genetic variant in our series (65%) as well as in literature [2–4,6,10,11,14,15]. Other frequent *CYP21A2* variants identified in patients with NC-CAH are Pro30Leu, Pro453Ser, Arg339His, Arg369Trp, Ile230Thr. *CYP21A2* genotyping indicates that several individuals with NC-CAH are compound heterozygotes for different variants in the two alleles, harboring one classic and one non-classic mutations or two non-classic alleles; the other ones are homozygous for two mild mutations (Table 1) [2,4,8–10]. Different combinations of genetic variants can yield different severity of clinical phenotypes [3,4].

A patient with genetic proven NC-CAH had a 1/240 chance of having a child with C-CAH; the risk for patients with a compound heterozygosity was calculated at 1/360 [6].

2. Clinical Findings

Individuals with NC-CAH may be asymptomatic (cryptic forms) [2,6] and they are usually identified through family studies mainly in male sex [9]. The reason why some patients are asymptomatic at the time of diagnosis is not well defined. Indeed, individual hypothalamic-pituitary-adrenal axis responsiveness to stressful environmental stimuli, peripheral sensitivity to androgens, epigenetic factors, the possibility of diagnosis before clear clinical manifestations could be involved [9].

In symptomatic patients, clinical manifestations are variable; main signs and symptoms are related to age-related androgen excess in both sexes (Table 3). Higher psychological stress related to hyperandrogenism is present in females at all ages [2,5,6].

At birth, children of both sexes with NC-CAH are asymptomatic, because genital virilization do not occur as well as adrenal crisis. Premature development of pubic and/or axillary hair (or premature adrenarche) is the more frequent feature in girls as in boys (Table 3). Adrenarche is considered premature if it appears before the age of eight years in girls and nine years in boys. In the large majority of children, premature adrenarche represents an anticipation of the prepubertal physiologic adrenarche and it is characterized by slight elevation of serum dehydroepiandrosterone sulfate. In addition, premature adrenarche could also be a manifestation of an increased sensitivity of the hair follicle to normal androgen levels. Finally, premature adrenarche represents the first clinical manifestation and the first clinical sign for suspicion of NC-CAH in a minority of children with premature development of pubic/axillary hair (5–30%). In fact, it is present in 50–80% of patients with NC-CAH, mainly when pediatric series are considered [6,8–17]. Mild clitoral hypertrophy may occur in girls. Additional signs of androgen excess are acne and hirsutism; they may be severe and usually develop during adolescence [17–19]. Moran et al. [19] reported that after the age 10 years hirsutism was present in 59% and acne in 33% of affected females. Hirsutism may worsen with age [19]. In a multicentric German study, Dörr et al. [11] showed no significant phenotypical differences among children grouped according to their genotype (severe/mild or mild/mild). They also showed that heterozygous children might present with no significant phenotypical differences [11].

Table 3. Non-classic congenital adrenal hyperplasia (CAH): main clinical findings in girls and boys according to cumulative data in large pediatric series [8–12,14,17].

Feature	Females	Males
Premature pubarche and/or premature onset of axillary hair	+	+
Prepubertal tall stature in respect to mid-parental height	+	+
Increased growth velocity for chronological age	+	+
Advanced bone age	+	+
Central precocious puberty *	+	+
Severe acne	+	+
Hirsutism	+	–
Polycystic ovary syndrome (adolescent girls/adult women)	+	–
Testicular ectopic adrenal rests	–	rare
Irregular cycles	+	–
Oily hair in girls/male pattern balding (in late adolescence/adulthood)	+	–
Impaired adult height	+	+

+ = clinical finding present; – = clinical finding does not present in this sex. Patients with genotype C/Null or C/A show more severe clinical picture than those with genotype C/B or C/C (see Table 1 for definition of genotypes). * Central precocious puberty may be a consequence of advanced bone age; its onset may occur after the start of hydrocortisone treatment [9,10,16].

In addition, recent data suggest that digenic heterozygous variants in genes controlling adrenal steroidogenesis may present phenotypically as NC-CAH [20]. These authors reported a 30-year-old woman with hyperandrogenism and borderline elevated 17-OHP levels (see below) harboring double genetic variants in *CYP21A2* and in *CYP11B1* genes, the latter is causative of a very rare form of CAH [20]. Thus, larger genetic investigation should be likely carried out in patients with indicative clinical and/or endocrine data, but only a heterozygous variant in *CYP21A2*.

Prepubertal or pubertal gynecomastia is poorly recognized finding limited to male sex of NC-CAH due to *CYP21A2* mutations [21].

Prepubertal tall stature and advancement of bone age over chronological age are main additional findings in both sexes [8–12]. However, impaired final height may occur in adulthood due to the increased bone age in childhood [5,17,22,23]. Some years ago, Brunelli et al. [23] reported that children with NC-CAH had poorer height outcome in comparison with C-CAH (both SV and SW), because they underwent to sub-optimal or late treatment. On the contrary, New et al. [24] found that final height in untreated patients with NC-CAH resulted significantly greater than for C-CAH, albeit individual adult heights were significantly below their mid-parental height [24]. Recent large pediatric series confirmed significant low adult height of children with NC-CAH (n = 122) in comparison with their mid-parental height (-0.7 ± 0.9 SDS and -0.4 ± 0.7 SDS, respectively; $p = 0.005$) [8]. Other authors showed that adult height and target height was not significantly different in both sexes (females -0.36 ± 1.05 SDS vs. -0.38 ± 0.86 SDS; males -0.34 ± 1.06 SDS vs. -0.38 ± 0.91 SDS) [12]. Early diagnosis and early commencement of hydrocortisone treatment has been claimed to improve adult height in children with NC-CAH; indeed, a trend toward better outcome in untreated patients than in those who underwent hydrocortisone therapy have been reported in two retrospective multicentric studies (Table 4). Likely, severity of phenotype, genotype, lag-time before diagnosis, adequacy of hydrocortisone doses and adherence to therapy (see below), retrospective design of most studies may be involved in the different end-results.

Table 4. Non-Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Adult height (AH) in large pediatric series of children treated with hydrocortisone or untreated.

	Hydrocortisone Treated				Untreated			
Authors	***n***	**AH, SDS**	**AH-MPH, SDS**	***p***	***n***	**AH, SDS**	**AH-MPH, SDS**	***p***
Eyal et al. [8]	66	−0.9 ± 0.8	−0.4 ± 0.7	0.03	49	−0.3 ± 1.1	−0.05 ± 0.8	NS
Wasniewska et al. [12]	171	−0.4 ± 1.0	−0.3 ± 0.9	–	21	−0.3 ± 1.4	0.6 ± 1.1	–

AH = adult height; AH-MPH = adult height–mid-parental height. NS = not signicant; – = not provided.

The development of central precocious puberty/early progressive puberty has been reported in 5–13% of girls with NC-CAH [9,10]. Signs and symptoms of central puberty may appear after the initiation of glucocorticoid treatment, when the hypothalamic GnRH pulse generator prematurely resumes pulsatile GnRH secretion leading to increased LH and FSH secretion with increased gonadal steroid production. The onset of central precocious puberty may be due to maturational effects of excessive adrenal steroid secretion, abrupt decrease of adrenal sex steroids and/or advanced skeletal maturation associated with NC-CAH. Proper management of this evenience may be an additional factor involved in long-term height outcome, but this issue will be better evaluated by additional prospective trials on homogenous selected patients.

From metabolic point of view, a recent review and meta-analysis [including 20 observational studies (14 longitudinal, 6 cross-sectional) with a moderate to high risk of bias] concluded that individuals with CAH demonstrate a high prevalence of cardiovascular and metabolic risk factors [25]. Limited data are available for children with NC-CAH. De Vries et al. [13] performed a retrospective, cross-sectional analysis of 114 patients (92 females; age at diagnosis 7.9 ± 4.2 years, age at last follow-up 17.1 ± 6.9 years). They concluded that NC-CAH diagnosed in childhood, whether treated or untreated, is not associated with an increased risk of overweight, obesity, or metabolic derangement; higher rate of systolic hypertension was found [13]. Recently, Delai et al. reported that insulin resistance was present in adolescent/young adult patients with NC-CAH (25 females, 6 males) investigated by insulin-euglycemic clamp and it was related to prolonged use and long-acting glucorticoid treatment [26]. Ben Simon et al. [27], by studying 75 subjects (49 females) with NC-CAH (61 hydrocortisone-treated and 14 untreated) as well as 134 healthy sex- and age-matched controls, reported that children and adolescents with NC-CAH have a body composition characterized by an imbalance between muscle and fat tissues, which may place them at increased risk for early-onset cardio-metabolic derangements. Glucocorticoid therapy did not appear to adversely affect their body composition [27]. Albeit, long-term prospective studies should be warranted to better assess these issues in NC-CAH, it seems appropriate to recommend periodic metabolic follow-up, healthy lifestyle indications in both treated and untreated children to prevent the long-term risk of obesity, hypertension and abnormal body composition [6,13].

Females with NC-CAH may present in adolescence and adulthood with amenorrhea (primary or secondary), chronic anovulation, infertility and a polycystic ovary morphology [2,9]. They may have greater risk of fertility problems in comparison with healthy females, in part due to ovulatory dysfunction. Treatment with oral contraceptives may restore menstrual cyclicity in those females not seeking fertility, but early treatment with hydrocortisone should be considered to decrease the risk of persistent anovulation [2,4,6,28]. Males with NC-CAH have relatively normal gonadal function and sperm counts. However, cases of oligospermia have been reported. Ectopic adrenal rests located in the testes (testicular adrenal rests tumor or TARTS) may be involved, albeit TARTS are usually associated with C-CAH instead of NC-CAH [1,6]. Recently, TARTS has been documented in 17–30% of male patients with *CYP21A2* gene variants, of whom the majority (80–95%) displayed the SV form, but also two males with the NC-CAH showed TARTS [29,30]. TARTS likely originate from residual adrenal cells; then, the increased ACTH levels stimulate these cells

to proliferate and form masses. An increasing prevalence has been observed from pubertal onset onward and their frequency in prepubertal years remains largely unknown [1,29,30]. Although they are benign, the growing masses would compress the spermatogonium and ductulus efferens, which may lead to irreversible damage. Glucocorticoid therapy can reverse both TARTS and fertility issues [29,30], but is unclear if early prepubertal start of hydrocortisone treatment may improve long-term fertility in adulthood.

3. Diagnosis

Diagnosis of NC-CAH may be not easy. Several individuals remain undiagnosed, because they are asymptomatic, or they show poor symptoms, or they are not rightly evaluated [2,6,22,28].

From endocrine point of view, all enzymatic defects within the steroidogenic pathway generate an increased precursor to product ratio, which is enhanced by ACTH stimulation. The prominent elevation of the main substrate for the defective enzyme forms the basis for hormonal diagnosis of CAH [1,2]. The diagnosis of 21OH deficiency relies on increased baseline or stimulated 17-OHP values [1,2]. Baseline 17-OHP values over 10 ng/mL (or >30 nmol/L) is considered diagnostic for 21-OH deficiency, while a baseline value of 17-OHP below 2.0 ng/mL (<6 nmol/L) between 8.00 and 10.00 a.m. should exclude 21-OH deficiency [22,31]. These indications do not always reflect clinical findings in our and other pediatric series (Table 5), suggesting that ACTH testing should be performed when clinical data are suggestive of NC-CAH [32]. Intravenous ACTH stimulation test [dose according to age: <1 month = 36 μg/kg (or 250 μg/m^2 body surface area), 1–6 months = 62.5 μg; 6 months–2 years = 125 μg; >2 years = 250 μg; blood sampling at 0 and 60 min.) is regarded as the gold standard to confirm the biochemical diagnosis of NC-CAH [1,2,4–6,14,28]. A 17-OHP peak between 10 and 100 ng/mL (30–300 nmol/L) is considered diagnostic for NC-CAH [22,31,33]. Even if mean 17-OHP values resulted higher in genetic proven children with NC-CAH than in proven heterozygous subjects, some our and other data [11] indicates that stimulated 17-OHP levels > 10 ng/mL does not definitely separate heterozygous carriers from patients with NC-CAH by using standard commercial laboratory techniques to assay 17-OHP. Thus, the assessment of baseline values only may impair the possibility to reach 100% diagnoses. In addition, some patients with genetic proven NC-CAH showed ACTH stimulated peak levels below 10 ng/mL in some series (Table 5).

Table 5. Non-classic congenital adrenal hyperplasia: basal and ACTH stimulated values of 17-OHP in children with genetic proven diagnosis.

Authors	17OHP, ng/mL *			
	Mean Baseline Values	**≤2.0 ng/mL, %**	**ACTH Stimulated Peak**	**≤10.0 ng/mL, %**
Livadas et al. [9]	9.4 (4.9–22.9) °	2.1	32.5 (25.0–52.5) °	none
Savas-Erdeve et al. [10]	11.6 (0.2–78.1) ^	NR	21.0 (5.3–168.6) ^	7.0
Dörr et al. [11]	14.5 (0.3–112) ^	3.8 ^^	61.1 ± 79.9 §	none
Baronio et al. [32]	43.9 (1.1–56.1)	16.6	44.0 (33.7–74.1)	none
Personal experience (unpublished)	10.0 (0.9–16.5) ^	22.0	45.2 (3.5–91.7)	12.0

* To convert ng/mL to nm/L multiply by 3.03; ° median and interquartile range; ^ mean and range; ^^ of patients with proven molecular diagnosis; § mean ± SD.

A complete steroid profile by liquid chromatography-tandem mass spectrometry (LC-MS/MS) should be performed to optimize diagnosis [6,31,33–35]. The assessment of 11-oxyandrogens may be new biomarkers to better individuate the adrenal androgen excess [34], because adrenals are they major source [36]. Some recent data reported that 11-oxyandrogen levels were disproportionately elevated relative to conventional androgens in patients with confirmed NC-CAH in comparison with individuals without CAH; 50%

of the latters had polycystic ovarian syndrome [36]. By their experience in adult women with androgen excess, other authors suggested that both measurement of 21-deoxycortisol and 17OHP by LC-MS/MS should provide sufficiently valid diagnostic discrimination between heterozygous carriers and patients with NCCAH [37]. These authors also stated that specific LC-MS/MS thresholds must be established, because they are lower than those previously determined by immunoassays [37]. However, the latter techniques remains available in selected laboratories or used in research programs and well defined normative values during pediatric age and pubertal stages will be provided.

Genetic testing is not considered as a first-line diagnostic tool for NC-CAH [31,33]. However, it is helpful to confirm the diagnosis, when endocrine data are inconclusive. In addition, *CYP21A2* genotyping allows to identify the genetic basis of the disease, that may be due to severe/mild allelic variants or mild/mild allelic variants. Genotyping also permits differential diagnosis, carrier detection and optimal genetic counseling, selecting individuals who carry an allele encoding a severe defect in *CYP21A2* [6,31,33].

4. Treatment

Hydrocortisone (usual dosage 10–15 mg/m^2 by mouth) is the gold standard for substitutive glucocorticoid treatment in children with C-CAH, owing to its short half-life and its lowest growth suppressing effect of available glucocorticoids [16,22,31,33,35]. However, glucocorticoid therapy in NC-CAH remains a debated issue.

Hydrocortisone is not recommended in asymptomatic patients [6,28,31,33,35]. In symptomatic children, indications for treatment are early onset and rapid progression of pubarche with bone age advancement over statural growth, leading to impaired predicted adult height. In girls, additional indications are virilization of external genitalia and irregular cycles after menarche [2,5,6,16,22,28,33]. Treatment with low dose hydrocortisone should be considered also to improve symptomatic hyperandrogenism in female sex [2,9,31,33,34]. In fact, severe acne and hirsutism are major causes of concern in adolescent girls, but they may require months to improve under glucocorticoid treatment. At this regard, other pharmacological treatments, as antiandrogens or estro-progestin pills, should be alternative options [6].

Stress doses of steroids for NC-CAH may be taken into consideration when cortisol levels fall below borderline values after ACTH stimulation test [15–18 ng/mL (45–54 nmol/L)], but they are not needed in persons with NC-CAH who have a normal cortisol response after ACTH stimulation [6,33]. Endocrine Society guideline suggest to monitor glucocorticoid replacement mainly using clinical parameters as body weight, blood pressure, energy levels and signs of glucocorticoid excess [31].

In Europe, oral hydrocortisone is available in 10 mg tablets that must subdivided to obtain doses adequate for babies and young children, rising risks of not voluntary over- or under-treatment. Taste of hydrocortisone may be an additional problem.

In the last years, a pediatric formulation of hydrocortisone has been registered and commercialized. It based on granules of hydrocortisone enclosed in capsules for opening, which are available as 0.5 mg, 1.0 mg, 2.0 mg and 5.0 mg. These formulations allow better dosing as well as they mask of the bitter taste of hydrocortisone, which is particularly useful in very young patients [38,39]. Recently, Neumann et al. [40] demonstrated that these new formulations permitted accurate dosing, better management from birth onward, and normal growth pattern without occurrence of adrenal crises in prepubertal children.

An additional new hydrocortisone formulation in modified-release capsules (5 and 10 mg) is now available for adolescents (age > 12 years) [41]. The total daily dosage is subdivided in two doses, of which two thirds are administered at bedtime and the remaining in the morning. A phase 3 study on 122 patients (age 19–69 years) showed improvement of the biochemical control of the disease, permitting reduction of corticosteroid dosage and subjective clinical benefit [41]. Twenty-four hour monitoring of androstenedione and 17OHP in patients treated with hydrocortisone in the classic 10 mg formulation or with the new modified-release drug has proven that the second allows to maintain concentrations

not significantly different compared with the first, but without the excessive increase in the morning hours [41]. An extension of the study up to 18 months showed that this advantage is maintained over time [41]. Intermediate long-acting steroids (as prednisolone) could be also considered in adolescents after attainment of adult height, but their use is associated with higher risk of adverse effects as impaired bone health and obesity [33].

In children with NC-CAH and no signs of genital virilization and normal endogenous cortisol production, an alternative approach to hydrocortisone treatment has been recently proposed that does not affect hypothalamic-pituitary-adrenal axis. Liu et al. [42] used aromatase inhibitors (anastrozole: 1 mg daily), which block the aromatization of androgen to estrogens, in three pre-pubertal girls with a diagnosis of NC-CAH. They found that monotherapy with anastrozole can be an effective in slowing down bone maturation and improving height outcomes [42]. Indeed, this alternative approach will be explored by additional well-designed clinical trials before its use in practice.

Central precocious puberty may develop in some children with NC-CAH during diagnostic process, during follow-up or after the beginning of glucocorticoid treatment (~5–13%) [9,10]. These cases benefit from adjunctive treatment with GnRH agonist analogs (GnRHa) [10]. Guven et al. [43] demonstrated that GnRHa treatment was the most important factor to optimize growth pattern in the patients with CAH complicated by the occurrence of central precocious puberty. Such therapy was able to slow down bone age advancement and to improve predicted adult height, bringing the latter closer to the target height expected from the genetic potentials. These authors also showed that bone age at initiation of GnRHa therapy was the most important parameter affecting the growth velocity and that height at diagnosis was inversely correlated with the ratio of bone age to chronological age at last visit [43].

5. Conclusions

NC-CAH is one of the most frequent endocrine autosomal recessive disorders in humans [6,7]. Early diagnosis remains disappointing, mainly in male sex because some symptoms are less alarming in boys than in girls. The typical symptoms worsen with aging (premature pubarche, hirsutism, acne, oligomenorrhea in females, TARTS in males), possibly leading to fertility problems in adulthood. Increased genetic risk of offspring affected by C-CAH is present in adults with NC-CAH carrying a severe allelic variant of *CYP21A2*. To optimize outcome some points will be addressed as:

- The awareness of family pediatricians and general practitioners on high prevalence of this disease, to improve early diagnoses.
- The improvement of hormonal screening by establishing more accurate basal and stimulated 17-OHP cut-off values for pediatric age not derived from adult studies. At this regard, the more expanded use of new techniques (as LC-MS/MS) in clinical laboratories and the setup of new biomarkers of adrenal androgen excess (as 11-oxyandrogens or 21-deoxycortisol) will offer better guidance to select individuals for genetic testing and to monitor management.
- The criteria to start early hydrocortisone treatment in children will be improved to achieve sound data on benefits and risks. Alternative therapeutic approaches should be explored, too.
- Comparative long-term trials will be developed, comparing “old” and “new” hydrocortisone formulations to obtain better cost/benefit profiles.

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