CONSENSUS

Consensus Statement on 21-Hydroxylase Deficiency from The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology

JOINT LWPES/ESPE CAH WORKING GROUP

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Despite over 50 yr of experience with steroid replacement therapy, the management of congenital adrenal hyperplasia (CAH) remains difficult, and clinical practice varies substantially throughout the world. To consider the evidence for best practice, to formulate management guidelines, and to consider innovative therapies, The Lawson Wilkins Pediatric Endocrine Society (LWPES) and The European Society for Pediatric Endocrinology (ESPE) convened a meeting in Gloucester, MA, March 14–17, 2002. The 40 participating physicians, psychologists, scientists, and surgeons from 12 countries on 4 continents agreed with the following consensus statement; this statement is concerned exclusively with CAH caused by 21-hydroxylase deficiency and does not address the other, rarer forms of CAH.

Neonatal diagnosis and treatment

The newborn female with CAH and ambiguous external genitalia requires urgent expert medical attention. The ambiguity is highly distressing to the family; therefore, immediate comprehensive evaluation is needed by referral to, or a visit by, a pediatric endocrinologist. An important goal is to ensure that the parents develop a positive relationship with their child. A well-organized multidisciplinary team (including specialists in pediatric endocrinology, psychosocial services, pediatric surgery/urology, and genetics) is essential for the diagnosis and management of the infant with ambiguous genitalia. It is important that the coordinator of the team has experience in the long-term care of the patient with CAH and provides a consistent message to the parents.

Clinical evaluation in term and premature neonates. Every newborn with ambiguous genitalia, a suspected diagnosis of CAH, or an abnormal result in a newborn screen for 17-hydroxyprogesterone (17OHP) should be evaluated by a pediatric endocrinologist. The evaluation of an infant with ambiguous genitalia includes a complete history, a physical examination, a reliable ultrasound investigation of the internal genitalia and adrenals, karyotype or fluorescence in situ hybridization for sex chromosome material, and a rapid, reliable plasma or serum measurement of 17OHP. Premature newborns may need serial measurements of 17OHP to differentiate false positive results from affected infants with CAH.

Newborn screening for CAH. Neonatal mass screening for 21-hydroxylase deficiency identifies both male and female affected infants, prevents incorrect sex assignment, and decreases mortality and morbidity (1–4). Therefore, newborn screening for CAH is beneficial and is recommended. Newborn screening is sufficiently specific and sensitive to detect almost all infants with classical CAH and some infants with nonclassical CAH (NCCAH). Sampling of blood spots should be performed, ideally between 48 and 72 h of age, and sent to the screening laboratory without delay. At present, direct binding assays for blood-spot 17OHP are the only practical method for screening.

Each screening laboratory needs to establish validated cutoff levels related to gestational age and birth weight, because 17OHP levels decline with increasing gestational age. Only laboratories with excellent internal and external quality control, demonstrated accuracy, and a rapid turnaround time on a large number of samples should be used. The laboratory should report immediately any abnormal result to the physician responsible for the patient.

A reliable CAH screening program requires both clinical evaluation and laboratory investigation for diagnostic confirmation. A positive screening result needs to be confirmed either by a validated 17OHP measurement of a second serum/plasma sample, a urine sample for a steroid profile, or analysis of the CYP21 gene. Newborn screening, using 17OHP, may detect other forms of CAH. In uncertain cases, additional specific tests are required. Measurements of androstenedione, aldosterone, cortisol, and testosterone by direct immunoassays are of limited value for diagnosis in the newborn.

Abbreviations: BP, Blood pressure; CAH, congenital adrenal hyperplasia; ESPE, European Society for Pediatric Endocrinology; HC, hydrocortisone; 11β-HSD, 11β-hydroxysteroid dehydrogenase; LWPES, Lawson Wilkins Pediatric Endocrine Society; NCCAH, nonclassical CAH; 17OHP, 17-hydroxyprogesterone; PRA, plasma renin activity.
CYP21 analysis. Molecular genetic analysis is not essential for the diagnosis but may be helpful to confirm the basis of the defect, to aid in genetic counseling, and to establish the diagnosis in uncertain cases. Ten mutations account for 90–95% of the affected alleles, but molecular genetic analysis is complicated by multiple copies of the genes and the possibility of multiple mutations on one allele (5, 6). The clinical features may not correlate with the genetic mutation in a small percentage of cases. Parental DNA samples are essential to segregate alleles.

Diagnosis of salt-wasting CAH. Salt wasters may not be apparent in the first days, or even weeks, after birth by electrolyte measurements. Salt wasters may be differentiated from simple virilizers by serial serum/plasma and/or urine electrolytes, plasma renin activity (PRA) or direct renin, and the results of CYP21 molecular analysis.

Prenatal diagnosis and treatment

Prenatal treatment has been advocated for fetuses at risk for classic CAH but is not appropriate for nonclassic CAH. The appropriateness, ethics, and outcomes of the prenatal treatment of CAH with dexamethasone remain controversial (7, 8). However, based on more than 200 fetuses treated to term and more than 1000 partially treated fetuses, it is clear that very early institution of treatment ameliorates the genital virilization in all affected females and completely eliminates it in more than 85% (7, 9). Variations in outcome may be attributable to starting treatment late, interruption of treatment, and individual differences in dexamethasone metabolism and androgen sensitivity. No consistent untoward effects have been reported, and birth weight is not reduced. However, few treated fetuses have reached adulthood, and long-term prospective studies have not been done. Thus, all agree that the results to date are very good, but long-term safety has not yet been proven in patients treated to term or in the 7 of 8 fetuses in whom treatment is stopped because they are male or unaffected.

Treated mothers experience greater weight gain, edema, and striae than untreated mothers, but present data do not show increased risk of hypertension or gestational diabetes (9).

Feto/maternal glucocorticoid physiology and pharmacology are poorly understood. Available data indicate that human fetal cortisol levels are low, approximately 20 nm or 0.7 μg/dl (10); the administered dose of dexamethasone may result in fetal concentrations of glucocorticoid that greatly exceed normal levels. However, the data on serum cortisol values in the fetus are scanty, and fetal serum dexamethasone values have not been reported.

Several recent reports have raised concerns about the use of short-term, very-high-dose glucocorticoids in late pregnancy or in premature infants (11). Animal studies have reported numerous complications from long-term, high-dose treatment of pregnant rodents and primates. Treatment of pregnant rats with 20 μg/kg-d dexamethasone was associated with decreased birth weight and adult hypertension, whereas similar treatment of pregnant sheep caused no apparent complications. However, the relevance of any of these studies to human physiology is not known.

Components of a prenatal treatment program include pre pregnancy genetic counseling and genotyping of the proband and parents, followed by diagnosis on fetal DNA obtained by chorionic villous biopsy. Fetal sex should be determined by Y chromosome PCR or karyotype. Allele-specific PCR should identify at least 90% of affected alleles. This number can be increased to nearly 100% with microsatellite analysis; Southern blotting; and, occasionally, DNA sequencing (5, 6). Competent core laboratories should study large numbers of samples.

Inclusion criteria for prenatal treatment include: 1) a previously affected sibling or first-degree relative with known mutations causing classic CAH, proven by DNA analysis; 2) reasonable expectation that the father is the same as the proband’s; 3) availability of rapid, high-quality genetic analysis; 4) therapy started less than 9 wk after the last menstrual period; 5) no plans for therapeutic abortion; and 6) reasonable expectation of patient compliance. The optimal dosage and timing is 20 μg/kg maternal body weight-d, in three divided doses, starting as soon as pregnancy is confirmed, and no later than 9 wk after the last menstrual period.

Treatment is continued to term in the affected female fetus and discontinued in all other fetuses. Maternal blood pressure (BP), weight, glycosuria, HbA1C plasma cortisol, dehydroepiandrosterone sulfate, and androstenedione should be measured initially and then every 2 months, adding plasma or urinary estriol after 15–20 wk of gestation.

There is substantial difference of opinion concerning whether prenatal treatment of CAH is a research endeavor. However, all are agreed that this requires a team consisting of a pediatric endocrinologist, an expert in high-risk obstetrics, a genetic counselor, and a reliable molecular genetics laboratory. It is not the “standard of care” for obstetricians in the community.

The treatment of 7 out of 8 fetuses who cannot be helped by prenatal treatment creates an ethical dilemma for which there is no clear answer, and parents should be aware of this. We believe that this specialized and demanding therapy should be undertaken by designated teams using nationally or multinational protocols, subject to institutional review boards or ethics committees in recognized centers. Written informed consent must be obtained after the balanced review of the risks and benefits of treatment. Families and clinicians should be obliged to undertake prospective follow-up of prenatally treated children whether they have CAH or not. The data should be entered into a central database audited by an independent safety committee.

Study protocols should consider all psychological/behavioral and somatic effects of excess prenatal glucocorticoids and androgens that have been observed in animal experiments or in human studies. Long-term follow-up into late adolescence is mandatory. Relevant control populations should be identified. These studies should also include the partially treated fetuses. Funding agencies, such as the National Institutes of Health or the European Commission, should be encouraged to support such long-term studies.

Surgical management and psychological issues

Genital surgery. The decision about surgery should be made by the parents, together with the clinical team, after complete
disclosure of all relevant clinical information and all available options have been discussed and after informed consent has been obtained. The goals of surgery are: 1) genital appearance compatible with gender; 2) unobstructed urinary emptying without incontinence or infections; and 3) good adult sexual and reproductive function.

Once a decision has been made to raise a newborn as female, surgery for those with virilized genitalia caused by CAH is recommended when the patient has a high proximal junction between the vagina and urethra (12, 13). Surgery on infants with ambiguous genitalia requires a high degree of expertise and should only be performed in centers with significant experience. Based on recent clinical experience, the recommended time for surgery is at age 2–6 months; although, at present, this is not universal practice. It is important to note that surgery at this stage is technically easier than at later stages.

When the degree of virilization is less (minimal clitoromegaly and the junction between the vagina and urethra near the perineum), surgery may not be necessary. In such cases, the decision to operate should be based on appropriate contrast studies of the urinary tract and examination under anesthesia, with cystoscopy. Surgery to reduce clitoral size requires careful consideration. Total removal of the clitoris should never be performed. If clitoral reduction is elected, it is crucial to preserve the neurovascular bundle, the glans, and the preputial skin related to the glans (14, 15). The early operation should be a one-stage complete repair using the newest techniques of vaginoplasty, clitoral, and labial surgery (12–14, 16) and should be carried out at a center with experience of at least 3–4 cases/yr. Revision vaginoplasty is often required at adolescence, and the timing should be decided with the patient and family. Patients who wish to consider further procedures should be treated by a surgeon experienced in the current techniques.

Surgery between the age of 12 months and adolescence is not recommended in the absence of complications causing medical problems. Vaginal dilatations are contraindicated at this stage, although this procedure is often useful in adolescence and in adulthood. Repeated genital examinations should be minimized. Genital photography should be discouraged and only be done with parental consent and, except in infancy, performed only under anesthesia.

At each designated center, one surgical team should be responsible for all surgery involving ambiguous genitalia. There should be close cooperation between centers to broaden experience, to audit results, and to allow adequate evaluation of outcomes. We acknowledge that there are concerns about early surgery. However, surgical techniques have improved. We urge caution in judging outcome from outdated procedures. Systematic studies are needed to evaluate ultimate function for all girls undergoing surgery.

It is recognized that 46, XX children with significant virilization may present at a later age. Consideration for sex reassignment must be undertaken only after thorough psychological evaluation of patient and family. Surgery appropriate to gender assignment should be undertaken after a period of endocrine treatment.

Psychological issues. Females with CAH show behavioral masculinization, most pronounced in gender role behavior, less so in sexual orientation, and rarely in gender identity (17–19). Even in females with psychosexual problems, general psychological adjustment seems to be similar to that of females without CAH. Currently, there is insufficient evidence to support rearing a 46, XX infant at Prader stage 5 as male. Whereas studies of women whose surgery was performed 20–30 yr ago indicate a range of psychosexual difficulties, there is reason for optimism that outcome will be better with current surgical and medical treatment. We recognize a need for greater availability of professional psychological services and support groups for patients and families. Decisions concerning sex assignment and associated genital surgery must consider the culture in which a child and her/his family are embedded. As the pace of societal change, including the flexibility of gender role, increases, more frequent review of management policies and long-term outcomes is important.

Treatment considerations in patients with CAH

Optimal glucocorticoid dosing. Recognizing that treatment does not mimic physiologic secretion, the goal is to replace deficient steroids while minimizing adrenal sex hormone and glucocorticoid excess, preventing virilization, optimizing growth, and protecting potential fertility. Outcome is not always ideal. Consensus is based on clinical experience. During infancy, initial reduction of markedly elevated adrenal sex hormones may require up to 25 mg hydrocortisone (HC)/m²·d, but typical dosing is 10–15 mg/m²·d divided three times daily. HC oral suspension is not recommended (20); divided or crushed tablets of HC should be used in growing children. Cortisone acetate requires conversion to cortisol for bioactivity (21); HC is considered the drug of first choice. Excessive doses, especially during infancy, may cause persistent growth suppression, obesity, and other Cushinoid features. Therefore, complete adrenal suppression should be avoided. Insufficient data exist to recommend higher morning or evening dosages.

Whereas HC is preferred during infancy and childhood, long-acting glucocorticoids may be an option at or near the completion of linear growth. Prednisone and prednisolone need to be given twice daily. Prednisolone may be preferable, because this is the active drug. The dose (2–4 mg/m²·d) should be approximately one fifth the dose of HC. The dosage of dexamethasone is 0.25–0.375 mg/m²·d, given once daily. Monitoring of these more potent glucocorticoids should include BP, in addition to weight, and other clinical and laboratory variables. These steroids have minimal mineralocorticoid effect, compared with HC. In children with advanced bone age, such as in boys with nonsalt-losing CAH, initiation of therapy may precipitate central precocious puberty, requiring treatment with a GnRH agonist.

Mineralocorticoid use. All classic CAH patients should be treated with fludrocortisone at diagnosis in the newborn period. Dosage requirements in early infancy range from 0.05–0.30 mg/d, whereas typical maintenance doses are 0.05–0.2 mg/d, depending on the sodium intake. Such therapy will reduce vasopressin and ACTH levels and lower the
dosage of glucocorticoid required. The need for continuing mineralocorticoids should be assessed based on PRA and BP (22). Sodium chloride supplements are often needed in infancy, at 1–3 gm/d (17–51 mEq/d), distributed in several feedings (23).

Criteria for the diagnosis and treatment of NCCAH. The standard method of diagnosis involves a 60-min stimulation test with (1–24)ACTH. However, a single early-morning (before 0800 h) level of 17OHP may also serve as a fairly reliable screening tool. Treatment is only recommended for symptomatic patients [e.g., those with an advanced bone age coupled with a poor height prediction (compared with the family target height), hirsutism, severe acne, menstrual irregularities, testicular masses, and (in the young adult) infertility].

Monitoring treatment for classic CAH. Monitoring may be accomplished based on physical and hormonal findings suggestive of excessive or inadequate steroid therapy. Laboratory measurements may include serum/plasma electrolytes, serum 17OHP, androstenedione, and/or testosterone, and PRA or direct renin, every 3 months during infancy and every 4–12 months thereafter. The time from the last glucocorticoid dose should be noted; the diurnal rhythm of the adrenal axis should be taken into account. Patients receiving adequate replacement therapy may have hormone levels above the normal range. Alternative measurements include urinary metabolites (pregnanetriol) or filter paper blood and salivary hormones. Ideally, laboratory data will indicate a need for dose adjustments before physical changes, growth, and skeletal maturation indicate inadequate or excessive dosing.

Stress dosing. Patients with CAH should carry medical identification and information concerning therapy for stress. Caregivers should have an emergency supply of im HC or glucocorticoid suppositories. Because circulating levels of cortisol normally increase during stress, patients should be given increased doses of glucocorticoids during febrile illness (>38.5°C/101°F), when vomiting or when unable to take oral feedings, after trauma, and before surgery. Participation in endurance sports may also require extra steroid dosing. Mental and emotional stress, such as school examinations, does not require increased dosing.

Stress dosing should be 2–3 times the maintenance glucocorticoid dose for patients able to take oral medications. Surgical and trauma patients and those unable to take oral steroids require rectal or parenteral HC. Glucose concentrations should be monitored, and iv sodium and glucose replacement may be required. Surgical or trauma patients may receive rectal, im, or iv HC. When practical, an iv bolus may be followed by continuous iv infusion of HC. Guidelines for iv bolus and subsequent dosage are as follows: for children younger than 3 yr of age, 25 mg followed by 25–30 mg/d; for children 3–12 yr of age, 50 mg followed by 50–60 mg/d; and for adolescents and adults, 100 mg followed by 100 mg/d (24).

Resources for patients and families with CAH. Official CAH websites, videos, and pamphlets should be developed by LWPE and ESPE and made available to other pediatric endocrine societies. Examples of websites potentially useful as family resources include: <www.hopkinsmedicine.org/pediatricendocrinology/patient.html> and <www.rch.unimelb.edu.au/publication/cah_book/index.html>.

Management of classical CAH and NCCAH in adolescence

Physical and genital examinations over the life span. The prior practice of frequent genital examinations in females should be abandoned. Therefore, unless there is clinical or laboratory evidence of poor control or one seeks to assess the pubertal progress and size of the clitoris, genital examinations should not be performed. In adolescent females or if questions arise regarding the progress of puberty, the use of tampons, or initiation of sexual intercourse, genital examination with attention to the adequacy of the vaginal introitus may need to be performed. Most importantly, the patient and/or her family should be appraised of the reasons for the examinations (25).

Safeguarding psychological well-being. Psychological assessment and support of the patient (with both classic and NCCAH) and his/her family should be a routine component of the comprehensive care and management of these patients. Parents and/or patients should be offered the option of age- and sex-appropriate psychologic counseling at the time of the initial diagnosis. Counseling regarding sexual function, future surgeries, gender role, and issues related to living with a chronic disorder should be addressed.

Management issues during transition of care of the young adult patient. Traditionally, the pediatric endocrinologist directly or indirectly cares for infants, children, and adolescents with CAH. In late adolescence or even early adulthood, care is usually transferred to an internal medicine (adult) endocrinologist in the same institution or clinical setting. We recommend that a transition team should also include, as needed, a gynecologist, a urologist, and a psychologist with specific expertise and interest in the treatment of such patients.

Adult males should be counseled that compliance with treatment is important to enhance normal fertility and reduce the risk of a palpable testicular mass (26). Although frequently found by sonography, testicular masses may not be of clinical importance. Nonetheless, we recommend periodic physical examinations and, as indicated, hormonal measurements, sonography, and magnetic resonance imaging of both testes to assist in delineating the extent of such lesions. Surgical removal of a glucocorticoid unresponsive nodule may be effective in preserving or improving fertility (27).

The effectiveness of the genital repair in adolescent and adult women needs to be assessed, and vaginal stenosis should be repaired. Counseling about anxiety, depression, dyspareunia, and other sexual matters, as well as contraception, is useful (28).

Women with NCCAH should be counseled regarding an increased risk of infertility. However, the actual numerical risk is not available and may vary depending on the ethnic background and degree of overlap with polycystic ovarian
syndrome. The risk of women with CAH or NCCAH having an affected fetus is low.

Management of a CAH woman in pregnancy. Pregnant women with CAH should be monitored and delivered in a tertiary center equipped and experienced to handle such pregnancies. Glucocorticoids that do not cross the placenta, such as HC and prednisolone, should be used. Dexamethasone should be avoided (except when used in prenatal therapy). Glucocorticoid doses should be adjusted to maintain maternal serum testosterone concentrations near the upper range of normal for pregnancy (29). When reconstructive surgery has been performed, we recommend elective cesarean section to avoid damage to the genital tract. When cesarean section is performed, doses of HC have to be increased before and tapered after delivery. A pediatrician should be present during delivery to take care of the newborn and to initiate diagnostic procedures when an affected child is expected according to the results of prenatal testing (30, 31).

Experimental therapies and future developments

The place of adrenalectomy in CAH. Bilateral adrenalectomy by laparoscopy is effective in decreasing adrenal androgens and the likelihood of iatrogenic hypercortisolemia (32, 33). It should be considered only in cases where conventional therapy is failing. Vigilance in maintaining regular substitution of HC and fludrocortisone is mandatory, with prompt institution of stress dosages at the onset of illness. The patient must be monitored, throughout life, for activation of ectopic adrenal rest tissue. The procedure should only be carried out where long-term follow-up is secured, and in the form of ethically approved clinical studies.

CRH antagonists for adrenal suppression in CAH. The use of CRH antagonists in CAH is promising on theoretical grounds but awaits future developments of drugs with improved pharmacological properties.

Treatment with antiandrogens and aromatase inhibitors in addition to HC and fludrocortisone. Based on the success of an earlier approach in familial male sexual precocity, it was hypothesized that the deleterious effects of elevated androgens on adult height could be prevented by using an antiandrogen to block androgen action and/or an aromatase inhibitor to block conversion of androgen to estrogen. Limited short-term (2 yr) studies in CAH show improved control of height velocity and bone maturation at reduced glucocorticoid dosage (34). Long-term safety data are not available, and reproductive effects are not known. Liver function has to be carefully monitored.

Epinephrine deficiency in CAH. Patients with CAH suffer from varying degrees of dysplasia and dysfunction of the adrenal medulla, expressed primarily as epinephrine deficiency (35). This may play a role in response to stress. Possible therapeutic implications are under study.

Innovative genetic approaches. Preimplantation genetic diagnosis for CAH is possible, but further research is required to determine its utility. Gene therapy is currently not possible in humans with this disorder.

DHEA replacement in CAH. CAH patients on glucocorticoid treatment have low DHEA levels. Studies in adult patients with Addison’s disease have shown beneficial effects of DHEA replacement (36), but the relevance in CAH is unknown.

11β-Hydroxysteroid dehydrogenase (11β-HSD) inhibitors in CAH. 11β-HSD inhibitors have the potential for modulating tissue-specific activity of glucocorticoids (37). At present, there are no specific compounds that are selective inhibitors of 11β-HSD type I or type II, and clinical experience with nonspecific 11β-HSD inhibitors is limited. Therefore, the use of these inhibitors cannot be recommended, at present.

GH treatment with or without administration of GnRH agonists. A meta-analysis of 561 patients with CAH (the majority with 21OH deficiency) revealed an overall mean final height SD score of −1.4 (38). Thus, an acceptable height is achieved by many patients with CAH, and the mean adult height deficit is substantially less than frequently thought. However, some CAH patients fail to reach normal adult height. A small group of short CAH patients have been treated with GH for 2 yr, either alone or in combination with a GnRH agonist. This significantly improved growth rate and predicted final height (39), but adult height data are not yet available.

Conclusions

These guidelines are designed to cover all aspects of the management of this complex disease in children, from diagnosis through adulthood. The multidisciplinary nature of management is emphasized, with the recognition that such expert teams need appropriate reimbursement and governmental support. There remain important deficits in our knowledge about this disorder; and again, these have been highlighted. New therapeutic strategies are emerging but, as yet, require longer evaluation before being introduced into routine practice. In the meantime, we should focus on early diagnosis, optimal medical and surgical treatment, and attention to compliance.

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