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Congenital adrenal hyperplasia: an update in children

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Abstract

Purpose of review—Congenital adrenal hyperplasia (CAH) in children, the majority of which is due to 21-hydroxylase deficiency, represents a group of disorders in which there is impaired cortisol synthesis and abnormalities in adrenal hormonal profiles. There continues to be debate regarding the optimal management of and treatment for these children. This review will highlight the most recent advances in neonatal screening for CAH, as well as the timeliest recommendations for the treatment and management of 21-hydroxylase deficiency, both the classic and non-classic forms of the disorder.

Recent findings—Substantive advancements have been made with regards to neonatal screening for CAH, allowing for earlier diagnosis while minimizing the morbidity and mortality associated with delayed detection. While the achievement of normal growth and development remains the ultimate goal of treatment, recent studies have provided further insight into the management and refinement of therapy in these children.

Summary—The optimal management and treatment for children with CAH is still unclear. While there have been recent advances in the diagnosis and treatment of this group of disorders, there is still much to learn in order to optimize therapy for these individuals.

Keywords

21-hydroxylase deficiency; congenital adrenal hyperplasia; neonatal screening; non-classic congenital adrenal hyperplasia

Introduction

The term congenital adrenal hyperplasia (CAH) describes a family of autosomal recessive disorders in which there is impaired cortisol synthesis due to a deficiency in one of the enzymatic steps required for cortisol production (1). Due to the disordered enzymatic step, cortisol production is decreased, while ACTH is increased via a negative feedback loop, and there can be both overproduction of the hormones prior to the enzymatic block and/or deficiency of those hormones distal to the disordered enzymatic step. CAH is a rare disorder with a reported incidence of 1:10,000–1:20,000 births, although there is increased prevalence in certain ethnic groups (2–5).

21-hydroxylase deficiency, in which there are mutations in *CYP21A2,* the gene encoding the adrenal 21-hydroxylase enzyme, is the most common form of CAH and accounts for

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>90% of all patients with CAH (6,7). In this disorder, as a result of the deficient enzyme, there is impaired conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and progesterone to deoxycorticosterone (DOC), essential steps in the pathway to cortisol and aldosterone synthesis. The symptoms of CAH depend upon which hormones are affected as a result of the enzymatic block. In classic 21-hydroxylase deficiency, there is impaired cortisol production as well as overproduction of adrenal androgen precursors and adrenal androgens. The diagnostic hormone is 17-hydroxyprogesterone, which is markedly elevated in 21-hydroxylase deficiency. The excess androgen production results in virilization, a hallmark of this disorder. Additionally, 75% of patients with classic CAH will also have aldosterone deficiency which can result in salt-wasting crisis in infancy manifested by profound hyponatremia, hyperkalemia, and shock (8•).

A non-classic form of 21-hydroxylase deficiency has also been described in which salt-wasting is absent and in the female, genitalia are typically normal in appearance at birth (9). Evidence of androgen excess includes rapid growth, early appearance of pubic hair, and acne. Non-classic CAH presents in childhood, adolescence, or young adult life. The non-classic form of the disorder is more prevalent with 0.1–0.2% of the Caucasian population being affected and may occur in up to 1–2% of certain inbred populations (10).

This review will discuss advances in neonatal screening for CAH, as well as the most current treatment and management guidelines for 21-hydroxylase deficiency, both the classic and non-classic forms of the disorder. The reader is also referred for a more in-depth review to the recent updated Endocrine Society CAH Clinical Practice Guidelines (11••).

Screening

Newborn screening for CAH is appropriate given that it is a relatively common disorder, which if left untreated, can result in significant morbidity and mortality, thus making early diagnosis essential. In 1977, the ability to measure 17-hydroxyprogesterone in a capillary blood specimen on filter paper became possible, which ushered in the start of newborn screening for CAH (12). All 50 states in the United States and at least 12 other countries screen for CAH as of 2009. Screening has been shown to shorten time to diagnosis of CAH in infants (13–16), which is of particular importance for male infants who are born without genital ambiguity and for completely virilized females. These infants are unlikely to be diagnosed promptly on a clinical basis alone. It has been shown that affected infants who are picked up by screening have less significant hyponatremia (16,17). Current screening methods, however, do result in many false-positive screens, which can be a source of stress and anxiety for families (18); as screening methods improve, this unintended consequence of screening should lessen.

First-tier screening for CAH involves the use of immunoassays to measure 17-hydroxyprogesterone from dried blood spots on the filter paper cards used for other neonatal screening tests. (3–5,19). Although RIA and ELISA have been used in the past, currently automated time-resolved-dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA) has become the method of choice for most states and European countries (8•,20). There are several limitations of first-tier screening. When undertaking interpretation of results, it is important to remember that 17-hydroxyprogesterone levels are normally high at the time of birth and decrease over the course of several days, whereas in affected infants with CAH, 17-hydroxyprogesterone levels rise over time. 17-hydroxyprogesterone levels also tend to be lower in female infants as compared to males, which reduces the sensitivity of the screening test (21). Also, infants who are premature, sick, or stressed tend to have higher levels of 17-hydroxyprogesterone compared to healthy term infants and this can result in an increased number of false-positive screens. In order to deal with these issues, most laboratories in the

United States use birth weight-adjusted cutoffs (8•,22,23); however, it has been shown that using gestational age may improve the sensitivity of the test since 17-hydroxyprogesterone levels correlate better with gestational age than weight (24). There are also concerns that antenatal corticosteroid treatment may reduce 17-hydroxyprogesterone levels; however effects have been inconsistent (25,26). In the case of non-classic CAH, screening methods that employ the measurement of 17-hydroxyprogesterone have been shown to only identify a handful of cases (27•).

In order to ensure a high level of sensitivity, cutoff values for 17-hydroxyprogesterone are set low such that approximately 1% of all tests are reported positive. Using such low cutoff values results in a situation in which only 1 in every 100 newborns with a positive screening test will have CAH (11••). To rectify this situation and reduce the number of infants who must undergo follow-up testing, either the cutoff value for 17-hydroxyprogesterone must be raised such that most cases of severe salt-wasting CAH will still be detected but there is a risk for missing as many as 30% cases of simple virilizing CAH (15,28) or else a second tier of screening be instituted as proposed by the recent consensus guidelines (11••).

Molecular genetic testing and biochemical testing have both been proposed for second-tier screening. *CYP21A2* mutations can be ascertained from DNA obtained from the same dried blood spots used for various screening tests. Since 10 mutations (deletions or conversion events) are responsible for greater than 90% mutant alleles, individuals who test negative for any mutations are unlikely to be affected. Those who have at least one mutation would need to be evaluated further. While studies have shown that genotyping may augment screening for hormonal measurements, there is no widespread study proving its efficacy as a second-tier screen (29–32). It is also costly and time-consuming as compared to biochemical testing. In addition, the focus on a single gene means that it would not be a helpful method to diagnose other enzymatic deficiencies responsible for CAH (11••).

Liquid chromatography followed by tandem spectrometry (LC-MS/MS) appears to be a more promising technology for second-tier screening and is able to address numerous issues that arise with the use of immunoassays (33,34). Measuring steroid ratios also improves the specificity of LC-MS/MS. Use of this two-tier approach for three years with LC-MS/MS as the second-tier screen improved the positive predictive value of CAH screening in Minnesota from 0.64 to 7.3% (35). A positive predictive value of 100% was achieved with a modified protocol that used the ratio of the sum of 17-hydroxyprogesterone and 21-deoxycortisol, divided by cortisol, in a German program. When the ratio was greater than 0.53, all 16 affected children were properly identified and there were no false-positive results out of 1609 samples that tested positive on initial screening (36). If the technology can be made more efficient, LC-MS/MS could even be used as a first screen for CAH (37).

If the results of newborn screening are positive for CAH, further follow-up is required. The availability of pediatric subspecialists in a particular geographic location may dictate who receives the initial referral: the primary care physician and/or pediatric endocrinologist. 17-hydoxyprogesterone levels that are only mildly elevated may just require a repeat filter paper specimen. However, if the 17-hydroxyprogesterone is markedly elevated and/or there is concern for clinical instability, urgent evaluation is warranted and serum electrolytes and 17-hydroxyprogesterone must be drawn (11••). Ultimately a cosyntropin stimulation test, using a dose of 0.125–0.25mg cosyntropin, is the gold standard for diagnosis of CAH (38); however, stimulation testing should never delay treatment when the diagnosis is strongly suspected and there is concern for electrolyte abnormalities or circulatory collapse. 17-hydroxyprogesterone can also be elevated in the setting of other enzymatic defects, especially 11β (beta)-hydroxylase deficiency, and may necessitate measuring other adrenal hormone levels as part of the evaluation when performing stimulation testing (39).

If the diagnosis of CAH is suspected after infancy, it is important to obtain an early morning baseline 17-hydroxyprogesterone level. The degree of elevation in 17-hydroxyprogesterone will often hint at the underlying diagnosis. If the 17-hydroxyprogesterone level is markedly elevated (>10,000 ng/dL), the diagnosis of classic CAH is likely, whereas levels >2000 ng/dL but <10,000 ng/dL typically reflect non-classic disease (11••). Measuring the full panel of adrenal hormones after cosyntropin stimulation testing is beneficial in helping to differentiate 21-hydroxylase deficiency from other enzyme defects.

Treatment

Reduction of excessive adrenal hormones and replacement of those hormones that are deficient remains the goal of treatment for CAH. Glucocorticoids have been used for over 50 years with the goal of preventing adrenal crisis and virilization, while allowing for normal growth and development. Administration of glucocorticoids reduces ACTH production, reverses adrenal hyperplasia, and reduces the levels of hormones in excess. Hydrocortisone in three daily divided doses remains the maintenance therapy of choice in growing patients with classic CAH. Hydrocortisone is recommended in childhood because of concerns regarding side-effect profile and risk for growth suppression with use of the longer-acting steroid preparations (40). The standard dose is typically in the range of 10–20 mg/m^2/day. Immediately postnatally, it may be necessary to exceed the recommended dose range in order to expeditiously lower markedly elevated adrenal hormone levels. When desired steroid levels are achieved, the dose can be quickly tapered (11••). It should also be noted that hydrocortisone suspension and tablets are not considered bioequivalent; adequate control may not be achievable with the oral suspension given the non-predictable distribution of the drug in liquid (41). In those patients who have nearly completed or completed their linear growth, the longer-acting steroid preparations such as prednisone or dexamethasone, may be used. There is currently much interest in alternative steroid replacement regimens with the intent of better simulating normal physiological cortisol secretion (42•). With severe 21-hydroxylase deficiency, there is an inability to increase cortisol levels during periods of stress and thus glucocorticoid doses must be increased during these episodes (11••).

Per current consensus guidelines, all infants who are diagnosed with classic CAH should be treated with a mineralocorticoid, such as fludrocortisone, as well as receiving sodium chloride supplementation (11••). The need for continued mineralocorticoid and sodium chloride supplementation must be periodically reassessed since recovery from salt-wasting has been documented in some patients (43•,44). It is extremely important to monitor blood pressure in all infants and children who are receiving mineralocorticoid supplementation.

In the case of non-classic CAH, the current recommendation is that asymptomatic patients do not require treatment with glucocorticoids. In fact, the vast majority of patients with non-classic CAH who are not on glucocorticoid therapy are able to mount an appropriate response to stress (45•). Treatment should be reserved for children and adolescents who are found to have significantly advanced skeletal maturation, which is predicted to negatively impact their adult height (11••,45•). Even for patients with premature pubarche, if the bone age is not advanced, treatment can be judiciously withheld as long as close monitoring is in place. Glucocorticoid therapy may also be beneficial for adolescents with menstrual irregularities and acne; however, hirsute individuals will typically require the addition of a third generation oral contraceptive with anti-androgenic potential for resolution of symptoms (46,47).

Monitoring

As stated above, the ultimate goal for the management of CAH is the attainment of normal growth and development, while minimizing symptomatology associated with the disorder. As such, regular assessment of height, weight and physical examination is crucial. Laboratory evaluation of adrenal androgens is useful in evaluating the effectiveness of treatment and should be consistently timed; 17-hydroxyprogesterone, androstenedione, and testosterone are considered the best markers when assessing the appropriateness of current glucocorticoid therapy and low normal levels may be an indication of over-treatment (11••). Annual bone ages to assess skeletal maturation are also important. Although it is known that chronic steroid use can lead to reduced bone mineral density, currently there are no studies to support this finding in children with CAH and as such routine evaluation of bone mineral density is not recommended (11••,48–50). There are insufficient data to support routine screening for adrenal masses since the majority of adrenal tumors in boys with CAH are testicular adrenal rest tumors, which are benign and often reduce in size when glucocorticoid therapy is refined (11••,51). Menstrual irregularities may be present, particularly when therapy is inadequate (52,53). Optimizing glucocorticoid treatment may be sufficient, although some females with well-controlled CAH experience a PCOS-type picture and may benefit from oral contraceptive therapy (54,55). For severely virilized females, genital surgery may be necessary. While there is still debate regarding the optimal age at which to perform such surgery, current recommendations are that patients should be referred to centers where there are experienced teams who perform these procedures regularly (11••). While it is known that adult height may be compromised in patients with CAH, currently growth hormone and drugs that delay pubertal progression are considered experimental and further studies must be undertaken (11••).

Conclusion

Congenital adrenal hyperplasia represents a group of disorders of steroidogenesis in which there is impaired cortisol production and abnormalities in the adrenal hormonal profile. Glucocorticoid and mineralocorticoid therapy continue to be a mainstay of treatment for classic CAH, although these drugs must be carefully titrated to avoid the possible side effects associated with over or under-treatment. Advances in newborn screening techniques have allowed for earlier diagnosis of CAH, while minimizing the morbidity and mortality that accompanied delayed recognition of the disorder. Although significant advances in the diagnosis and treatment of congenital adrenal hyperplasia have been made in recent decades, there is still much to learn about the optimal management and therapy for this group of disorders.

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Key Points

- Advances in newborn screening for CAH have allowed for earlier diagnosis of the disorder, while minimizing morbidity and mortality associated with delayed diagnosis
- Second tier-screening for CAH is recommended and LC-MS/MS shows promise as a second-tier screening method
- Glucocorticoid and mineralocorticoid therapy remain the mainstays of treatment for CAH
- Infants with classic CAH require treatment with glucocorticoids and mineralocorticoids, as well as sodium chloride supplementation
- Achievement of normal growth and development remains the utmost goal for the management and treatment of CAH