Emerging medical therapies for congenital adrenal hyperplasia
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Phyllis W. Speiser
Pediatrics, Zucker School of Medicine at Hofstra-Northwell Health, Lake Success, New York, 11042-2062, USA

Abstract
Congenital adrenal hyperplasia has traditionally been treated with daily oral doses of glucocorticoids and mineralocorticoid supplements. Such therapy does not precisely replicate the adrenal cortex's circadian pattern. As a consequence, patients are intermittently overtreated or undertreated leading to growth suppression in children, excess weight gain and altered metabolism. Several new treatments are on the horizon. This article will summarize some new potential therapies as adjuncts to, or replacement for, standard therapy.

Keywords
congenital adrenal hyperplasia, treatment
Introduction

Congenital adrenal hyperplasia (CAH) is caused by one of several inherited enzyme deficiencies. The most common form of the classic disorder, found in about 1:14,000 to 1:18,000 births, is steroid 21-hydroxylase deficiency. Mutations in CYP21A2 (P450c21) impair adrenocortical production of cortisol and frequently aldosterone and lead to the accumulation of adrenal sex steroids. Allelic variation accounts for most phenotypic differences. Cardinal features of classic CAH include atypical development of the external genitalia in girls with manifest virilization. Both males and females have salt wasting with failure to thrive and potentially fatal hypovolemia and shock. Newborn screening, now universal in the US and in many developed countries, can mitigate these complications (reviewed in 4). Despite life-saving glucocorticoid (GC) and mineralocorticoid (MC) oral therapies, treatment does not precisely replicate adrenal physiology. Individuals with CAH commonly experience adverse outcomes in terms of growth, metabolic, reproductive, and mental health endpoints. This discussion of emerging medical treatments will be restricted to the classic or severe forms of steroid 21-hydroxylase deficiency.

Improved glucocorticoid delivery

Normal adrenocortical secretion has a circadian rhythm quite distinct from that of blood cortisol levels achieved by administering two or three daily oral doses of GC medication. Hydrocortisone (HC) subcutaneous delivery for 6 months via a programmed pump in eight adults with classic CAH produced significant reduction in adrenal androgens with improvement in quality of life and fatigue. Though conceptually attractive and perhaps applicable to highly motivated patients who are inadequately managed by conventional treatment, pump management is complex. An early trial with a once-daily modified-release oral HC preparation (Chronocort, Diurnal, Cardiff, UK) given to 16 adults with classic CAH decreased adrenal androgen precursors despite a slightly reduced daily HC dose. However, subsequent phase 3 trials apparently failed to demonstrate superiority to standard HC treatment and this potential new treatment is currently on hold. A different type of modified-release GC (Plenadren, Shire, London, UK) is approved in Europe for adrenal insufficiency but has not been formally tested in CAH.

In the US, the lowest-dose HC tablet is 5 mg, and in Europe 10 mg, excessive for infants and young children. Availability of pediatric-dose formulations would eliminate concerns about improper compounding of HC from tablets. The European Medicines Agency has approved very-low-dose HC 1 mg granules (Alkindi, Diurnal) for treatment of adrenal insufficiency or CAH in infants and children. A US Food and Drug Administration new drug application is said to be pending.

Androgen/estrogen antagonists and synthesis inhibitors

To ameliorate the effects of adrenal androgen excess, females with CAH often need treatment additional to GC replacement. Such treatments may include dermatologic therapies for acne and hirsutism or additional hormone treatments (or both) to regulate menses or aid conception. All steroidogenic pathways to androgens and estrogens depend on activity of the enzyme 17-hydroxylase/17,20-lyase (P450c17, CYP17A1). Abiraterone acetate is an orally active, potent P450c17 inhibitor indicated for treatment of castration-resistant prostate cancer. Short-term adjunctive treatment with 250 mg/day abiraterone acetate (alongside standard steroid replacement) normalized the pre-dose serum androstenedione levels in all six women with poorly controlled classic CAH. Because abiraterone acetate also inhibits gonadal steroid production and could be teratogenic, its use in CAH would be limited to pre-pubertal children, women using contraceptives, or men who receive gonadal replacement. A clinical trial is under way in pre-pubertal children with CAH using contraceptives, or men who receive gonadal replacement. A clinical trial is under way in pre-pubertal children with CAH (ClinicalTrials.gov Identifier: NCT02574910) with the goal of minimizing exogenous GC and endogenous adrenal sex steroid hormone exposure in order to normalize growth and pubertal development.

Growth-promoting drugs

A systematic review and meta-analysis of adult height in individuals with classic CAH diagnosed before the age of 5 years included just over 1000 children in 35 studies that met the eligibility criteria. The pooled data indicated a corrected adult height standard deviation (SD) of −1.0. The average heights were 169 cm (66.5 inches) for men and 157 cm (61.8 inches) for women, both within the normal range for shorter than average adults in the general population. These data obviate the routine use of growth-promoting medications that are considered only for individuals whose heights were expected to be at least −2.25 SDs. Subgroup analysis revealed that the addition of early MC treatment was associated with increased height outcome.

A 2001 report tested growth hormone alone (n = 12) or in combination with leuprolide acetate (n = 8) to enhance growth in CAH patients with evidence of early puberty. Follow-up over 2 years showed improved predicted adult height, but as of this date, no data have been published to document actual adult heights. A proof-of-concept trial demonstrated that co-administration of growth hormone plus an aromatase inhibitor (again, alongside standard steroid replacement) improved adult height in a single adolescent male patient with CAH.

Since normal adult height may be achieved through judicious use of standard GC and MC therapies, further long-term prospective randomized and carefully controlled studies are needed to determine whether the use of growth-promoting drugs is safe and cost-effective in individuals with CAH. At present, such treatments are not considered standard care in children with CAH.

Other medical strategies

Reducing adrenocorticotropic hormone (ACTH) production is another mechanism for minimizing adrenal androgen excess. In a small trial of eight women with classic CAH, the selective corticotropin-releasing hormone receptor type 1 antagonist, NBI-77860, was added to conventional therapy, resulting in a more than 40% reduction in the morning ACTH surge and about 27% lower serum 17OHP. Variable reductions of androstenedione and testosterone were observed.
Mイトさんに、アドレナリノイドに使用される治療法の一種とされるアドレナケアクトミーをも考慮に入れ、アドレナリノイドに対する薬物の用量についても注意が必要である。

アドレナケアクトミー
アドレナケアクトミーは、女性のビリラリゼーションを引き起こす場合があり、特に一次的な薬物の用量が考慮されなければならない。この治療法は、生命脅威のある緊急のアドレナーザー性状態に対する対処として広く用いられている。

エピネフリン欠乏
エピネフリン欠乏を持つ成人の患者、特にクッシング症候群を有する患者には、過剰なアンドロゲンを含むGCSの使用が推奨されている。特に、アドレナケアクトミー後で、エピネフリンの欠乏が予想されるため、GCSの用量を適切に調整することが重要である。

ゲンマイテラピ
ゲンマイテラピは、遺伝子を変更し、目的とする腺細胞の機能を回復または改善する治療法である。この方法は、現時点では臨床的に有用な治療法ではないが、将来的に病気の診断や治療への新たな可能性を示唆するものである。

引用


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