Testicular Adrenal Rest Tumors in Boys and Young Adults with Congenital Adrenal Hyperplasia

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Purpose: Testicular adrenal rest tumors are a well-known complication in males who have congenital adrenal hyperplasia with potential infertility in adulthood. We assessed the prevalence of testicular adrenal rest tumors in infants to young men presenting to a CAH Comprehensive Care Center.

Materials and Methods: A total of 35 males with congenital adrenal hyperplasia due to 21-hydroxylase deficiency underwent scrotal ultrasonography, including 7 younger than 5 years, 9 who were 5 to 12 years old and 19 who were older than 12 years. Three and 35 patients had classic and nonclassic congenital adrenal hyperplasia, respectively. Bone age x-ray or advanced bone age x-ray history, glucocorticoid dose, fludrocortisone dose, and serum 17-hydroxyprogesterone, testosterone and androstenedione levels within 3 months of ultrasound were also recorded.

Results: Testicular adrenal rest tumors were detected in 5 of 35 patients (14%), including 1 of 9 (11%) who were 5 to 12 years old and 4 of 19 (21%) who were older than 12 years. The tumors were not detected in any patients younger than 5 years, including 1 infant with poor hormonal control. The youngest patients with positive findings was 6.6 years old. All patients with positive findings had bilateral disease and only 1 had suspicious physical findings. The glucocorticoid dose and 17-hydroxyprogesterone did not differ between patients with vs without a testicular adrenal rest tumor. Those with a tumor were more likely to have advanced bone age x-ray results (100% vs 42%, $p = 0.04$) and higher fludrocortisone dose ($p < 0.01$). All males with nonclassic congenital adrenal hyperplasia had negative tumor findings.

Conclusions: Testicular adrenal rest tumors were present in young males with classic congenital adrenal hyperplasia but not in infants or toddlers. These tumors were associated with higher fludrocortisone requirements and a history of advanced bone age x-ray results. However, the tumors did not develop in all poorly controlled males. Longitudinal studies are needed to understand the individual predisposition to testicular adrenal rest tumors and the age at which to begin screening patients with congenital adrenal hyperplasia.

Key Words: testis; adrenal hyperplasia, congenital; adrenal rest tumor; steroid 21-hydroxylase; mass screening

Abbreviations and Acronyms

17OHP = 17-hydroxyprogesterone

ACTH = adrenocorticotropic hormone

CAH = congenital adrenal hyperplasia

GC = glucocorticoid

TART = testicular adrenal rest tumor

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CONGENITAL adrenal hyperplasia is a potentially life-threatening form of primary adrenal insufficiency characterized by cortisol, aldosterone and epinephrine deficiencies as well as androgen excess.[1] It is most commonly caused by a mutation in the *CYP21A2* gene, which encodes the enzyme 21-hydroxylase, of which an absence or deficiency leads to reduced synthesis of cortisol and aldosterone, elevated ACTH, hyperplasia of the adrenal glands, accumulation of steroid precursors and excessive production of androgens (fig. 1).[2] [F1]

CAH is typically categorized as classic (severe) or nonclassic (mild, late onset). The classic salt-wasting form, which occurs in 67% of individuals with classic CAH, is characterized by a severe decrease in 21-hydroxylase activity, leading to almost complete deficiencies of cortisol and aldosterone, presentation at or soon after birth with ambiguous genitalia in females and the risk of early adrenal crisis if untreated.[3] The classic simple virilizing form, which occurs in 33% of individuals with classic CAH, is associated with 1% to 2% of normal 21-hydroxylase activity and still carries a risk of adrenal crisis but to a lesser degree than the salt-wasting form.[4] Nonclassic CAH is characterized by 20% to 50% of normal 21-hydroxylase activity, resulting in a milder phenotype.[5] The typical presentation occurs later in childhood or adolescence with findings secondary to androgen excess, including premature pubarche, growth acceleration, advanced bone age in growing children or hirsutism, acne, delayed menarche/menstrual irregularities and infertility among older patients.[6]

TARTs, which are a well-known complication in men with classic CAH due to 21-hydroxylase deficiency, can lead to gonadal dysfunction and infertility in adulthood.[7] The adrenal rest tissue in the testicle expresses ACTH specific receptors and is ACTH responsive, producing steroid hormones, and it can become hyperplastic.[8] A TART develops when there is growth of the adrenal rests within the testicular parenchyma. While the resulting tumors are benign, the location of most TARTs in the rete testis may lead to compressive effects with tubular obstruction and oligozoospermia/azoospermia.[7] In some cases a large TART can compress enough normal tissue to affect spermatogenesis and testosterone production.

Standard of care guidelines suggest that periodic screening should begin in adolescence.[9] However, specific recommendations vary and include screening younger children[10,11] with the suggestion that early detection is optimal.[7] While TARTs have been reported in children with CAH at a prevalence of 24% to 33%,[10,11] little is known regarding TART in infants and toddlers with CAH. A study of neonatal autopsies of boys with CAH noted the presence of ectopic adrenal tissue in 3 of 7 younger than 8 weeks and in 14 younger than 14 months.[12]

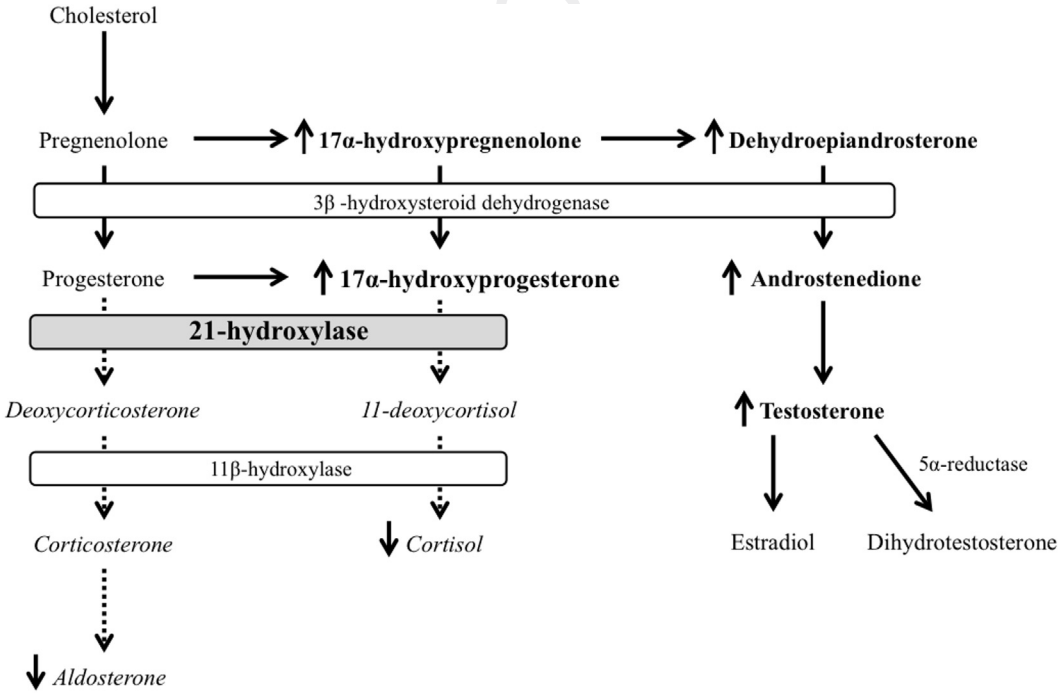

Figure 1. Adrenal gland steroidogenic pathway. Deficiency in enzyme 21-hydroxylase (shaded box) is most common cause of CAH, accounting for 95% of cases and leading to deficiencies in aldosterone and cortisol (dotted pathways). This results in accumulation of steroid precursors and excess androgen production (bold).