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Long-term outcome of testicular function in nonclassic lipid congenital adrenal hyperplasia

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BACKGROUND AND OBJECTIVE

Lipoid congenital adrenal hyperplasia (LCAH) is caused by mutations in STAR and characterized by defect in steroidogenesis and lipid droplet accumulation in steroidogenic cells. 46,XY patients with classic LCAH typically present with female-type external genitalia, while those with nonclassic LCAH have masculinized external genitalia. The rarity of the nonclassic form precludes the clarification of long-term outcomes of testicular function in nonclassic LCAH. The aim of this study was to report long-term outcome of testicular function in nonclassic LCAH.

CASE REPORTS

Case 1: At 1 year of age, hyperpigmentation was noticed for the lips and gradually spread to the skin and buccal mucosa. At 5 yrs, he was diagnosed with primary adrenal insufficiency (PAI) based on high plasma ACTH (> 6000 pg/mL) and low serum cortisol (1.7 µg/dL) levels and was subsequently treated with hydrocortisone (HC) and fludrocortisone (FC). Detailed information on pubertal development in this case was not available.

Case 2: At 4 yrs, hyperpigmentation of the skin was noticed when he had an episode of recurrent vomiting. He was diagnosed with PAI based on high plasma ACTH level (4600 pg/mL), low serum cortisol level (2.4 µg/dL), and high plasma renin activity (80.0 ng/mL/hr) and was subsequently treated with HC and FC. His testicular volumes increased to 3 mL at 11.3 yrs and gradually grew to 20 mL in the right and 12 mL in the left (Figure 2A).

Case 3: At birth, skin hyperpigmentation was already observed. At 5 hrs of life, he showed intermittent movements indicating seizure. Plasma glucose level was 26 mg/dL. He was diagnosed with PAI based on high plasma ACTH level (4858 pg/mL), low serum cortisol level (0.3 µg/dL), and high plasma renin activity (>80.0 ng/mL/hr) and was subsequently treated with HC and FC. His testicular volumes increased to 3 mL at 11.3 yrs of age and grew to 5 mL at 12.5 yrs, but did not increase further (Figure 2B).

Functional analysis of STAR: We assessed the hitherto undescribed activity of STAR-Arg272Cys to enhance pregnenolone production using in vitro analysis in COS-1 cells, which were co-transfected with a plasmid F2 expressing the NH2-CYP11A1-FDXR-FDX1 fusion protein, and revealed that STAR-Arg272Cys retained 35% of the wild-type STAR activity. This activity is consistent with those of other mutant proteins causing nonclassic LCAH ranging from 6% to 40%.

DISCUSSION

1) Adult testicular function of nonclassic LCAH

Based on our case series and review of the literature, all patients with nonclassic LCAH who developed normal male external genitalia completed pubertal development without androgen replacement therapy. However, their testicular function during adulthood was variable. Cases 1 and 2 did not show hypergonadotropic hypogonadism (HH), while Case 3 had compromised HH. Cases 2 and 3 had compromised spermatogenesis. Inconsistent with Case 2, Metherell et al. (#1) reported Case 4 who showed impaired fertility and no lipid accumulation in the cytosol of possibly hyperplastic Leydig cells at 36 yrs. The lipid accumulation may vary with age or otherwise depend on the residual activity of mutant STAR. The testosterone-producing capacity can be preserved in most males with nonclassic LCAH, indicating that STAR-dependent spermatogenesis is more important in adrenocortical cells than in fetal or adult Leydig cells.

2) Phenotypic variability of nonclassic LCAH

Our study addresses two important issues in the phenotype of nonclassic LCAH. There is no clear distinction between the classic and nonclassic forms with respect to the onset of PAI. Case 3 showed the earliest onset of PAI in nonclassic LCAH. The onset age of PAI likely depends on the timing and severity of physical stress. It is quite difficult to differentiate between these two forms of LCAH, especially in 46,XX females who exhibit female external genitalia regardless of the form of LCAH. Another issue is the phenotypic variability in testicular function between nonclassic male patients with the same STAR mutations. Steroidogenesis and spermatogenesis can be affected by other factors including cryptorchidism or variations in disease susceptibility genes. These results expand our knowledge of the genotypic and phenotypic variability of nonclassic LCAH.

CONCLUSION

Testosterone synthesis in nonclassic LCAH with normal male external genitalia can be sufficient for complete pubertal development and even to induce germ cell maturation despite lipid accumulation in the Leydig cells.

REFERENCES


Figure 1. Histopathology of the testis.

(A) Classic LCAH at 1 yr (not from the present report); (B) Case 2 at 5 yrs; and (C) Case 2 at 13 yrs. (A) and (B) were obtained by using light microscopy with hematoxylin-eosin (HE) staining; (C) was obtained by using electron microscopy (EM). Le, Leydig cell; N, nucleus.

Figure 2. Growth charts of testicular volume.


Table 1. Adult testicular function of males with nonclassic LCAH.

<table>
<thead>
<tr>
<th>Case</th>
<th>External genitalia</th>
<th>Pubertal development</th>
<th>Testicular volume (mL)</th>
<th>Pubic hair (Tanner stage)</th>
<th>LH</th>
<th>FSH</th>
<th>T</th>
<th>Semen volume (mL)</th>
<th>Spem cell count (c/µL · mL)</th>
<th>STAR genotype</th>
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<tbody>
<tr>
<td>1</td>
<td>Normal male</td>
<td>NA</td>
<td>Spontaneously completed</td>
<td>35.20 IV</td>
<td>5.2</td>
<td>3.7</td>
<td>4.4</td>
<td>38.60 4.00</td>
<td>Gly221Ser</td>
<td>Arg272Cys</td>
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<td>2</td>
<td>Normal male</td>
<td>11.1</td>
<td>Spontaneously completed</td>
<td>30.20 R20, L12.12 IV</td>
<td>8.4</td>
<td>90.6</td>
<td>26.9</td>
<td>10.70 18.70</td>
<td>Gly221Ser</td>
<td>Arg272Cys</td>
</tr>
<tr>
<td>3</td>
<td>Normal male</td>
<td>11.3</td>
<td>Spontaneously completed</td>
<td>20.50 I</td>
<td>18.4</td>
<td>3.2</td>
<td>5.0</td>
<td>31.20 3.10</td>
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<td>Arg272Cys</td>
</tr>
<tr>
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<td>Spontaneously completed</td>
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<td>2.8</td>
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<td>Arg272Cys</td>
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<td>Normal</td>
<td>15.00 NA</td>
<td>14</td>
<td>4.9</td>
<td>1.0</td>
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<td>Normal</td>
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<td>6.9</td>
<td>6.9</td>
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<td>0.78</td>
<td>32.00 3.20</td>
<td>Gly221Ser</td>
<td>Arg272Cys</td>
</tr>
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</table>

T, testosterone; NA, not available; R, right; and L, left.

*1. GnRH stimulation test
*2. SG stimulation test
*3. Cases 4 and 5 were reported in reference #1, Case 6 in #2, and Case 7 in #3.

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# Sex differentiation, gonads and gynecomastia or sex endocrinology

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