DSD 46,XY and serum steroid profile ambiguity due to combined 17-beta hydroxysteroid dehydrogenase/21-hydroxylase deficiencies

Authors: Elena Kuznetsova, Vitaliy Ioutsi, Anna Kolodkina, Natalia Kalinchenko, Anatoly Tiulpakov
Endocrinology Research Center, Moscow, Russian Federation

Objective and hypotheses. To describe and to characterize a case of DSD 46,XY presented with unusual serum steroid profile.
An 18-years-old professional female athlete is presented with primary amenorrhea.
Physical examination showed increased muscle mass, no breast development, male pattern of hair distribution, clitoris enlargement and blind-ending pseudo-vagina.
Ultrasound examination revealed bilateral inguinal gonads and no uterus.
Karyotype analysis showed 46,XY.
Hormonal examination revealed unusual serum steroid profile:
17-OHP 27.8 nmol/l (1.5-7.2);
DHEA-S 16.4 mkmol/l (0.9-11.7);
Testosterone 13.4 nmol/l (12-33);
Androstenedione 29.4 nmol/l (1.4-7.9).
LC-MS/MS was performed to clarify the diagnosis.

Steroid profile assayed by LC-MS/MS

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Result</th>
<th>Normal range (male references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-OHP</td>
<td>35.6 nmol/l</td>
<td>1.5–7.2 nmol/l</td>
</tr>
<tr>
<td>Cortisol</td>
<td>353 nmol/l</td>
<td>150-650 nmol/l</td>
</tr>
<tr>
<td>Androstenedione (A)</td>
<td>29.5 nmol/l</td>
<td>1.4–7.9 nmol/l</td>
</tr>
<tr>
<td>Testosterone (T)</td>
<td>12.9 nmol/l</td>
<td>12-33 nmol/l</td>
</tr>
<tr>
<td>Testosterone/Androstenedione</td>
<td>0.44</td>
<td>&gt;0.8</td>
</tr>
</tbody>
</table>

Genetic examination
(Sanger sequencing)
Sequencing of HSD17B3 gene showed a known pathogenic homozygous splicing mutation c.277+4A>T
Analysis of CYP21A2 gene revealed a homozygous p.V281L mutation, a frequent finding in non-classical congenital adrenal hyperplasia (NC CAH)

An accurate and comprehensive assessment of steroid hormones is pivotal for differential diagnosis of disorders of sex development (DSD) 46,XY, a part of which may be due to defects of testosterone biosynthesis.

Conclusion: To our knowledge, this is the first description of combined HSD17B3 and CYP21A2 deficiencies. Owing to the fact that NC CAH is frequent in certain populations, its contribution to observed peculiarities of phenotype and/or steroid profiles may be considered.