Late Diagnosis of 5-α-Reductase Type 2 Deficiency in an Adolescent Girl with Primary Amenorrhoea
Case report

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Abstract: Deficiency of the 5-α-reductase enzyme has been found to affect male sexual development. We report an 18-year-old patient who was referred to an endocrinology clinic in Jizan, Saudi Arabia, in April 2014 with primary amenorrhoea, virilisation and a lack of secondary sex characteristics. As female external genitalia were present at birth, she had been raised as a female. Magnetic resonance imaging revealed no uterine or ovarian tissue in the pelvis and the presence of a scrotal sac. She was diagnosed with 5-α-reductase type 2 deficiency, a 46,XY disorder of sexual development. Typically, affected males have pseudovaginal perineoscrotal hypospadias and ambiguous genitalia at birth. Individuals who have been raised as female manifest characteristics of virilisation at puberty, including deepening of the vocal tone, phallus enlargement, scrotal hyperpigmentation and increased muscle mass.

Keywords: 46, XY Disorders of Sex Development; Testosterone 5-alpha-Reductase; Dihydrotestosterone; Hypospadias; Puberty; Case Report; Saudi Arabia.

Case Report

An 18-year-old patient was referred to an endocrine clinic in Jizan, Saudi Arabia, in April 2014 with primary amenorrhoea, virilisation and a lack of secondary sex characteristics. As female external genitalia were present at birth, she had been raised as female. The patient reported vocal changes over the course of two years, which made her voice sound deeper and harsher. Additionally, over the previous year, she had experienced unusually thick hair growth on her upper and lower limbs as well as the axillary and inguinal regions. Her previous developmental history was normal. There was no history of consanguinity on the part of the parents.

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On physical examination, the patient communicated well, appeared to be comfortable and was not in any emotional distress. Her height was 162 cm, she weighed 68 kg and her body mass index was 25.9 kg/m². Hair was present on the extensor surfaces of her forearms and legs. Breast development corresponded to Tanner stage I, while pubic hair growth was categorized as Tanner stage III. Further physical examination revealed pseudovaginal perineoscrotal hypospadias and a blind vaginal pouch. The scrotal skin was rugose and pigmented with the right gonad palpable in the inguinal ligament. The left gonad was 3.2 cm and located in the labioscrotal pouch, while the phallus was 3 cm in length. The results of a hormonal assay are shown in Table 1.

Table 1: Hormonal assay results of an 18-year-old female patient with primary amenorrhoea, virilisation and a lack of secondary sex characteristics

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Result</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>FSH in mIU/mL</td>
<td>6</td>
<td>2–12</td>
</tr>
<tr>
<td>LH in mIU/mL</td>
<td>7</td>
<td>2–12</td>
</tr>
<tr>
<td>Cortisol in µg/dL</td>
<td>7.2</td>
<td>5.1–19.9</td>
</tr>
<tr>
<td>Estradiol in pg/mL</td>
<td>42.22</td>
<td>7.6–40.9</td>
</tr>
<tr>
<td>T in ng/dL</td>
<td>572</td>
<td>200–1,080</td>
</tr>
<tr>
<td>DHT in ng/dL</td>
<td>8</td>
<td>29–76</td>
</tr>
<tr>
<td>DHEA in µg/dL</td>
<td>126</td>
<td>22–640</td>
</tr>
<tr>
<td>AE in ng/dL</td>
<td>127</td>
<td>≤250</td>
</tr>
<tr>
<td>T/DHT ratio</td>
<td>67.8</td>
<td>8–16</td>
</tr>
<tr>
<td>17-OHP in ng/mL</td>
<td>0.8</td>
<td>0.1–1.4</td>
</tr>
</tbody>
</table>

FSH = follicle-stimulating hormone; LH = luteinising hormone; T = testosterone; DHT = dihydrotestosterone; DHEA = dehydroepiandrosterone; AE = androstenedione; OHP = hydroxyprogesterone.

Magnetic resonance imaging of the pelvis revealed no uterine or ovarian tissue. A scrotal sac was apparent and contained the left testis which measured 33 x 24 x 23 mm and was of normal shape and signal intensity [Figure 1A]. The undescended right testis was located in the right inguinal canal measuring 31 x 24 x 20 mm and was also of normal shape and signal intensity [Figure 1B]. The urinary bladder, urethra and seminal vesicles appeared normal. No prostatic tissue was identified. A final diagnosis was made of a 46,XY disorder of sexual development due to 5-α-reductase type 2 deficiency. After extensive counselling with the patient and her parents, the patient decided to undergo gender reassignment to become male.

Discussion

At birth, clinical symptoms of 5-α-reductase type 2 deficiency range from the appearance of female external genitalia to a nearly complete male phenotype; however, most patients who present with ambiguous genitalia are usually diagnosed in early infancy. The current case describes the late diagnosis of 5-α-reductase type 2 deficiency in an 18-year-old female patient presenting with primary amenorrhoea and characteristics of virilisation.

Young children with 5-α-reductase type 2 deficiency can either escape diagnosis or be misdiagnosed as having partial or complete androgen insensitivity syndrome. Since biochemical findings can be misleading, molecular testing is mandatory to identify the underlying cause of a disorder of sexual development. However, measurement of the basal serum concentration and the testosterone/DHT ratio after puberty is usually sufficient for an accurate assessment.
diagnosis of 5-α-reductase type 2 deficiency. In the present case, the diagnosis of 5-α-reductase 2 type 2 deficiency was based on the patient’s clinical presentation and a hormonal assay which revealed an abnormally elevated testosterone/DHT ratio of >60. Nevertheless, karyotyping and molecular studies are recommended to confirm a homozygous mutation of the SRD5A2 gene; unfortunately, this could not be performed in the current case.

Many 46,XY individuals raised as females will experience psychological difficulties during puberty, which results in most affected patients choosing to undergo gender reassignment to become male, as in the present case. In such cases, either DHT or high-dose testosterone therapy should be initiated so as to increase the size of the phallus. For patients diagnosed after infancy and whose gender identity is definitively female, a genitoplasty, prophylactic orchiectomy and oestrogen substitution therapy are recommended.

**Conclusion**

Although rare, 5-α-reductase type 2 deficiency should be suspected among female patients presenting with pubertal virilisation and primary amenorrhoea. Early recognition of this condition is critical to avoid psychological distress on the part of the patient, particularly after puberty. Molecular analysis of the SRD5A2 gene should be performed to confirm the diagnosis.

**References**