5-α-Reductase Deficiency Syndrome: An Experience from a Referral Hospital, Riyadh, Saudi Arabia

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Abstract

Background: 5-α-Reductase (5ARD) deficiency, is an autosomal recessive disease, resulting in the inability to produce the physiologically active DihydroTestosterone (DHT) which is required for normal virilization of the male external genitalia.

Material and Methods: This is a retrospective, hospital based study conducted over a 25 year period (1989-2014) at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, where patient’s files with 46 XY, DSD diagnosed with 5-α-reductase deficiency were reviewed for the clinical characteristics and management. All patients were managed by an experienced multidisciplinary team.

Results: During the period under review, a total of nine (16%) patients among the 56 patients, with 46 XY DSD were diagnosed hormonally, i.e. Human Chorionic Gonadotrophin (HCG) stimulated DHT / testosterone ratio of more than 35, to have 5-α-reductase deficiency. All patients presented with variable degrees of ambiguous genitalia. Unfortunately, three (33.3%) patients needed sex-reassignment. Their clinical characteristics and management were presented.

Conclusion: In our community, with an increased prevalence of consanguineous matings and with multiple siblings, it is not that uncommon to have such numbers of 5-α-reductase deficiency among those presenting with 46 XY DSD, and should be considered as an important differential diagnosis. A multi-disciplinary team approach is essential for a successful management and better prognosis.

Keywords: 5-α-reductase; Clinical Characteristics; Deficiency; Multi-Disciplinary; Sex-Reassignment
Introduction

5-α-reductase deficiency (5 ARD) is an autosomal recessive disorder, resulting in the inability to produce the physiologically active DiHydroTestosterone (DHT), which is required for the normal masculinization of the external male genitalia, in utero. Affected individuals are classically, born with ambiguous genitalia, however, variable degrees of virilization may occur. The uterus and fallopian tubes are absent due to normal production of the Mullerian-Inhibiting Factor (MIF). Testes are intact and are usually found in the inguinal canal or scrotum. Wolffian ducts differentiation is normal. Different mutations have been described [1-8].

Although frequencies for different countries are not established, increased frequency is reported in the Dominican Republic, New Guinea and in Turkey. This high frequency represents the effects of consanguinity in such communities. Most patients are identified in the neonatal period, being presented with ambiguous genitalia. However, some of these children are misdiagnosed as having partial or complete Androgen Insensitivity Syndrome (AIS), which can produce almost identical phenotypes. Delayed diagnosis can also occur in individuals with isolated clitoromegaly and otherwise normal female appearing external genitalia. In patients with this phenotype, diagnosis usually delayed until puberty when they present with primary amenorrhea and virilization [9-11]. In this report, we present our experience over a 25 year period (1989-2014), at the King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia.

Material and Methods

The study population included all patients presented to the endocrine service, King Khalid University Hospital, Riyadh, Saudi Arabia over a 25 year period (1989-2014), with 46 XY, Disorders of Sex Development (DSD) and found to have 5-α-reductase deficiency. The diagnosis was based on biochemical data of post-Human Chorionic Gonadotrophin (HCG) stimulation, Dihydrotestosterone Testosterone (DHT/T) ratio which is usually greater than 35. [12-14]. The King Khalid University Hospital (KKUH) is the main teaching hospital of the King Saud University and considered as one of the main referral hospitals in Riyadh, central of Saudi Arabia. The hospital provides primary, secondary, and tertiary health care services for the local population and also receives patients referral from all over the country.

The clinical notes of all patients with the diagnosis of 5-α-reductase deficiency were reviewed retrospectively. Data included history, clinical examination, the appropriate tests (radiological and hormonal evaluation) and management. All patients were managed by an experienced multi-disciplinary team which consists of a pediatric endocrinologist, neonatologist, geneticist, psychologist and a pediatric surgeon or urologist [14-15]. Ethical approved for this study was obtained from the Institutional Review Board (IRB), at King Khalid University Hospital.

Figure:

A patient with 46, XY DSD who was diagnosed with 5α-reductase deficiency. Note the virilization occurred at puberty.
Results
During the period under review January 1989 to December 2014, a total of nine patients were diagnosed hormonally, with 5-α-reductase deficiency among 56 (16%) patients presented with 46 XY, Disorder of Sex Development (DSD) being presented between birth to 12 years. Their clinical characteristics were shown in Table 1. Three (33.3%) patients were assigned initially a female sex and agreed for sex-re-assignment later on.

Table 1: Clinical characteristics in 9 patients with 5α-reductase deficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at initial diagnosis</th>
<th>Given sex</th>
<th>Clinical features</th>
<th>Sex of rearing and age</th>
<th>Family history</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Birth</td>
<td>Male</td>
<td>Ambiguous genitalia micropenis with chordee, bilateral undescended testicles</td>
<td>Male – 4 days</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Birth</td>
<td>Male</td>
<td>Hypospadias with chordee</td>
<td>Male – 4 days</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Birth</td>
<td>Male</td>
<td>Unilateral undescended testes Ambiguous genitalia</td>
<td>Male –4 days</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12 years</td>
<td>Female</td>
<td>Normal female genitalia with clitomegaly</td>
<td>Male –12 years</td>
<td>+ve</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6 month</td>
<td>Male</td>
<td>Hypospadias with bilateral undescended testes</td>
<td>Male – at birth</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 month</td>
<td>Male</td>
<td>Hypospadias with bilateral undescended testes</td>
<td>Male – at birth</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>8 years</td>
<td>Female</td>
<td>Normal female genitalia</td>
<td>Male – 8 years</td>
<td>+ve</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4 years</td>
<td>Female</td>
<td>Urogenital sinus with bifid, empty, scrotum</td>
<td>Male – 4 years</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1 year</td>
<td>Male</td>
<td>Micropenis with bilateral undescended testicle.</td>
<td>Male- at birth</td>
<td>-ve</td>
<td></td>
</tr>
</tbody>
</table>

All patients revealed no female internal structures with testis in variable positions (abdomen, inguinal canal and scrotum) by ultrasound or MRI, +ve (positive), -ve (negative)

Discussion
The 46, XY Disorders of Sex Development (DSD), are presently classified in three main categories; gonadal development defects, such as gonadal dysgenesis, gonadal biosynthesis and metabolism defects, such 5-α-reductase deficiency and gonadal disorders related to Androgen Insensitivity Syndrome (AIS). Genetic causes have been identified as loss of function mutations, responsible for 5-α-reductase deficiency type 2 deficiency which is one of the three 5-α-reductase isoforme expressed in humans. 5-α-reductase type 2 deficiency have variable phenotypes, ranging from a complete female phenotype at birth to a more or less complete virilization of genitalia. In girls with 5-α-reductase-2-deficiency, spontaneous virilization occurring at the onset of puberty usually reveals the condition [16-18]. In pubertal and adult individuals with the disease, very few studies of testicular histology showed severely altered spermatogenesis. This impairment could be related in part to cryptorchidism [17].

Most patients presented in the neonatal period, being presented with ambiguous genitalia, however, some patients are misdiagnosed, as in our series, and only diagnosed at puberty, being presented with masculinization and male habitus in somebody who reared as a female. Some patients, presented later on as delayed patients or primary amenorrhea and variable virilization of somebody who was reared as female. Clitomegaly
or microphallus with varying degrees of hypospadias also can be the first manifestation [7, 9-11].

Imaging with ultrasound and or Magnetic Resonance Imaging (MRI), will help in diagnosis [19-21]. Genetic studies can confirm the diagnosis, unfortunately, they were not available to us. The ratio of serum testosterone to dihydrotestosterone of greater than 35, can assure the diagnosis, after stimulation with Human Chorionic Gonadotrophin (HCG) [12, 13].

In a community, like Saudi Arabia, [22] with increased prevalence of consanguineous marriage and multiple siblings, it is not an unusual to see such numbers of 5-α-reductase deficiency. Two of them were siblings who at birth with ambiguous genitalia and given female sex, however, there diagnosis was questioned later on as the older child showed evidence of virilization at puberty.

In individuals, with 5-α-reductase deficiency, a male gender should be as further virilization occurs at puberty along with the development of a male habitus as in one of our patients. Many of these individuals will be fertile as adults assigned and the appropriate medical and surgical therapy should be given. Appropriate genetic and psychosocial counselling should be provided to the family and patients. All available information should be progressively disclosed [22-32].

References