Sultan Qaboos University Med J, May 2017, Vol. 17, Iss. 2, pp. e218–220, Epub. 20 Jun 17
Submitted 23 Oct 16
Revision Req. 14 Nov 16; Revision Recd. 11 Dec 16
Accepted 15 Jan 17
doi: 10.18295/squmj.2016.17.02.014

CASE REPORT

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

Case report

Abdul-Rahman A. Hummadi,[1] Ayel O. Yahya,[1] *Awad M. Al-Qahtani[2]

تشخيص متأخر للنوع الثاني من مرض نقص إنزيم 5-α-ريدوكتاس، لفتاة مراهقة مصابة بانقطاع الطمث الأولي

تقرير حالة

عبد الرحمن أحمد حمادي، عايل عمر يحيى، عوض محمد القحطاني

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.

الملخص: وجد أن نقص إنزيم 5-α-ريدوكتاس يؤثر على التطور الجنسي للذكور. سجلنا حالة عن مريضة تبلغ من العمر 18 عاما تم إحالتها إلى عيادة الغدد الصماء في جازان بالمملكة العربية السعودية، في أبريل 2014 مع انقطاع الطمث الأولي، والترجل، وعدم وجود خصائص جنسية ثانوية. وبما أن الأعضاء التناسلية الخارجية للإناث كانت حاضرة لها عند الولادة، فقد نشأت كأنثى. لم يكتشف التصوير بالرنين المغناطيسي أي نسيج للرحم أو المبيض في الحوض، وتبين وجود كيس الصفن. وتم تشخيصها بأنها مصابة بالنوع الثاني من مرض نقص إنزيم 5-α-ريدوكتاس، 46،XY وهو اضطراب في النمو الجنسي. عادة ما يكون لدى الذكور المتضررين مهبل كاذب وفتحة مجرى البول في كيس الصفن، وأعضاء تناسلية غير واضحة. ويظهر الأفراد الذين تمت تنشئتهم كإناث صفات الترجل في سن البلوغ، بما في ذلك خشونة الصوت، وتضخم العضو الذكري، وفرط تصبغ الصفن وزيادة كتلة العضلات.

الكلمات المفتاحية: 46،XY اضطرابات النمو الجنسية؛ التستوستيرون 5-ألفا-ريدوكتاس؛ ديهدروتستوسترون؛ فتحة مجرى البول في كيس الصفن؛ بلوغ؛ تقرير حالة؛ المملكة العربية السعودية.

The 5-α-reductase enzyme, also known as 3-oxo-5α-steroid 4-dehydrogenase, converts testosterone to the more physiologically active dihydrotestosterone (DHT).[1] A deficiency of 5-α-reductase results in a rare autosomal recessive 46,XY disorder of sexual development caused by mutations in the *steroid 5-α-reductase 2* (*SRD5A2*) gene located on chromosome 2p23.[1,2] Most affected individuals have female external genitalia present at birth and are raised as female; however, a few patients are adequately masculinised by childbirth and are raised as male.[2,3] Due to its rarity, the prevalence of 5-α-reductase type 2 deficiency in the general population is unknown.[4]

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.

[1]*Department of Endocrinology & Internal Medicine, King Fahad Central Hospital, Jizan, Saudi Arabia;* [2]*Department of Family & Community Medicine, College of Medicine, Najran University, Najran, Saudi Arabia*

**Corresponding Author e-mail: awadresearch17@gmail.com*

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/m^2. Hair was present on the *extensor* surfaces of her forearms and legs. Breast development corresponded to Tanner stage I, while pubic hair growth was categorised 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

Hormone	Result	Normal range	
		Males	Females
FSH in mIU/mL	6	2–12	2–12
LH in mIU/mL	7	2–12	2–12
Cortisol in µg/dL	7.2	5.1–19.9	5.1–19.9
Estradiol in pg/mL	42.22	7.6–40.9	12.5–163.5
T in ng/dL	572	200–1,080	10–70
DHT in ng/dL	8	29–76	22–380
DHEA in µg/dL	126	22–640	22–380
AE in ng/dL	127	≤250	≤250
T/DHT ratio	67.8	8–16	8–16
17-OHP in ng/mL	0.8	0.1–1.4	0.1–2.9

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

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.[5] 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.[6] Since biochemical findings can be misleading, molecular testing is mandatory to identify the underlying cause of a disorder of sexual development.[6,7] However, measurement of the basal serum concentration and the testosterone/DHT ratio after puberty is usually sufficient for an accurate

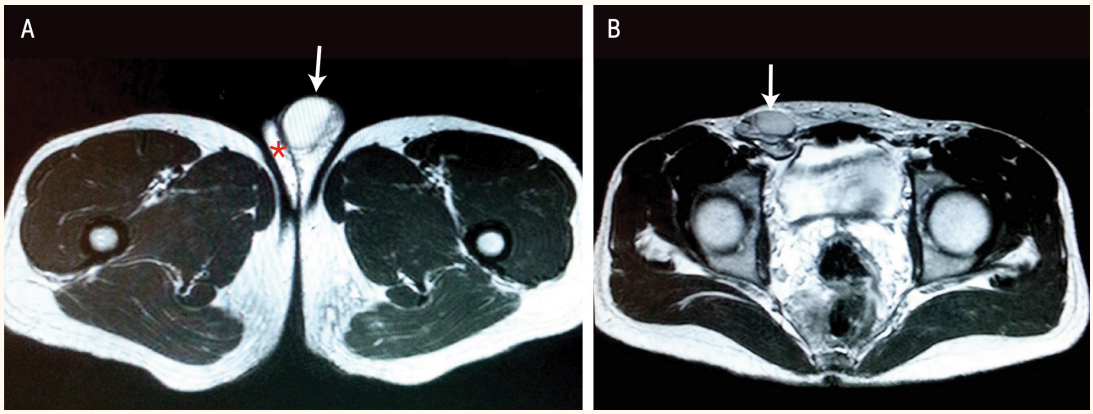

Figure 1: Magnetic resonance imaging (MRI) of the pelvis of an 18-year-old female patient with primary amenorrhoea, virilisation and a lack of secondary sex characteristics showing **(A)** no uterine or ovarian tissue and the presence of a scrotal sac (asterisk) containing a left *testis* of normal shape and signal intensity (arrow) and **(B)** an undescended right *testis* (arrow) in the right inguinal canal of normal shape and signal intensity.

diagnosis of 5-α-reductase type 2 deficiency.[8] 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.[4,7]

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.[9–11] 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.[12]

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

1. Fratianni CM, Imperato-McGinley J. The syndrome of 5[alpha]-reductase deficiency. Endocrinologist 1994; 4:302–14.
2. Genetics Home Reference. 5-alpha reductase deficiency. From: https://ghr.nlm.nih.gov/condition/5-alpha-reductase-deficiency Accessed: Dec 2016.
3. Hekimsoy Z, Hatipoglu O, Öz D, Alarslan P, Özmen B. 5-Alpha reductase type 2 deficiency: A case report. Endocr Abstr 2012; 29:P418.
4. Wilson JD, Griffin JE, Russell DW. Steroid 5 alpha-reductase 2 deficiency. Endocr Rev 1993; 14:577–93. doi: 10.1210/er.14.5.577.
5. Bertelloni S, Scaramuzzo RT, Parrini D, Baldinotti F, Tumini S, Ghirri P. Early diagnosis of 5alpha-reductase deficiency in newborns. Sex Dev 2007; 1:147–51. doi: 10.1159/000102103.
6. Walter KN, Kienzle FB, Frankenschmidt A, Hiort O, Wudy SA, van der Werf-Grohmann N, et al. Difficulties in diagnosis and treatment of 5alpha-reductase type 2 deficiency in a newborn with 46,XY DSD. Horm Res Paediatr 2010; 74:67–71. doi: 10.1159/000313372.
7. Skordis N, Neocleous V, Kyriakou A, Efstathiou E, Sertedaki A, Philibert P, et al. The IVS1-2A>G mutation in the SRD5A2 gene predominates in Cypriot patients with 5α reductase deficiency. J Endocrinol Invest 2010; 33:810–14. doi: 10.3275/7079.
8. Maleki N, Kalantar Hormozi M, Iranparvar Alamdari M, Tavosi Z. 5-alpha-reductase 2 deficiency in a woman with primary amenorrhea. Case Rep Endocrinol 2013; 2013:631060. doi: 10.1155/2013/631060.
9. Mendonca BB, Inacio M, Costa EM, Arnhold IJ, Silva FA, Nicolau W, et al. Male pseudohermaphroditism due to steroid 5alpha-reductase 2 deficiency: Diagnosis, psychological evaluation, and management. Medicine (Baltimore) 1996; 75:64–76. doi: 10.1097/00005792-199603000-00003.
10. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5alpha-reductase deficiency in man: An inherited form of male pseudohermaphroditism. Science 1974; 186:1213–15. doi: 10.1126/science.186.4170.1213.
11. Sinnecker GH, Hiort O, Dibbelt L, Albers N, Dörr HG, Hauss H, et al. Phenotypic classification of male pseudohermaphroditism due to steroid 5 alpha-reductase 2 deficiency. Am J Med Genet 1996; 63:223–30. doi: 10.1002/(SICI)1096-8628(19960503)63:1<223::AID-AJMG39>3.0.CO;2-O.
12. Conte FA, Grumbach MM. Abnormalities of sexual determination and differentiation. In: Greenspan FS, Gardner DG. Basic & Clinical Endocrinology, 7th ed. New York, USA: McGraw-Hill Medical, 2003. Pp. 564–607.