Endocrine (2012) 42:453–455
DOI 10.1007/s12020-012-9635-x

LETTER TO THE EDITOR

Puberty reveals a familial disorder of sex development

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Published online: 24 February 2012

An 18-year-old female born to consanguineous parents presented with primary amenorrhoea and urinary difficulties. Breast buds and pubic hair had appeared at the age of 16. She had three younger sisters with variable degrees of virilisation of the genitalia at birth and in whom the karyotype was 46, XY. Diagnostic work-up in the sisters was hampered by non-attendance, but analysis of the CAG repeat in the androgen receptor gene had excluded X-linkage.

She was hirsute and her breasts (Tanner stage 2) and pubic hair (Tanner stage 3) were underdeveloped. She had an enlarged clitoris, a small introitus and a blind-ending vagina. Bilateral masses, suggestive of gonads, were palpable in the inguinal canals. Her initial blood tests showed LH 8.6 U/l (NR 1.3–8.4 U/l), FSH 5.2 U/l (NR 2.9–8.4 U/l), oestradiol 105 pmol/l (NR 100–750 pmol/l), testosterone 8.6 nmol/l (NR < 2 nmol/l) and 17OH-progesterone 1.2 nmol/l. Her karyotype was 46, XY.

Magnetic resonance imaging (MRI) of the pelvis showed an absent uterus and upper 2/3 of the vagina, as well as atrophy of the lower third of the vagina. Gonads were identified in the inguinal region bilaterally (Fig. 1a–c). The initial diagnostic category was 46, XY disorder of sex development (DSD) in a partially virilised adult female with partial androgen insensitivity syndrome as a possible cause. However, this was unlikely in view of an X-linked disorder having been ruled out in the case of younger sisters. An LH (0 min—5.6 U/l; 20 min—56.4 U/l; 60 min—47.2 U/l) and FSH (0 min—6.9 U/l; 20 min—17.3 U/l; 60 min—17.1 U/l) incremental response to luteinising hormone-releasing hormone was consistent with puberty and an intact hypothalamic–pituitary–gonadal axis. Serum concentration of anti-Mullerian hormone (AMH) was 69.4 pmol/l (NR 0–37 pmol/l). This indicated the presence of testes. Human chorionic gonadotropin stimulation showed a peak testosterone response of 52.2 nmol/l which, together with the AMH level, confirmed the presence of testes. Furthermore, a raised testosterone to dihydrotestosterone (DHT) ratio of 20.9:1 suggested a diagnosis of 5 alpha-reductase deficiency. This was confirmed on a urinary steroid profile (USP) demonstrating low levels of the 5 alpha-reduced metabolites relative to the 5 beta-reduced epimers. Sequencing of the *SRD5A2* gene revealed a missense mutation in exon 4 which changed a glutamic acid to lysine (E200K). This mutation was subsequently confirmed in her affected sisters. The mutation has been reported as being pathogenic in causing 5 alpha-reductase deficiency. Our patient decided to continue

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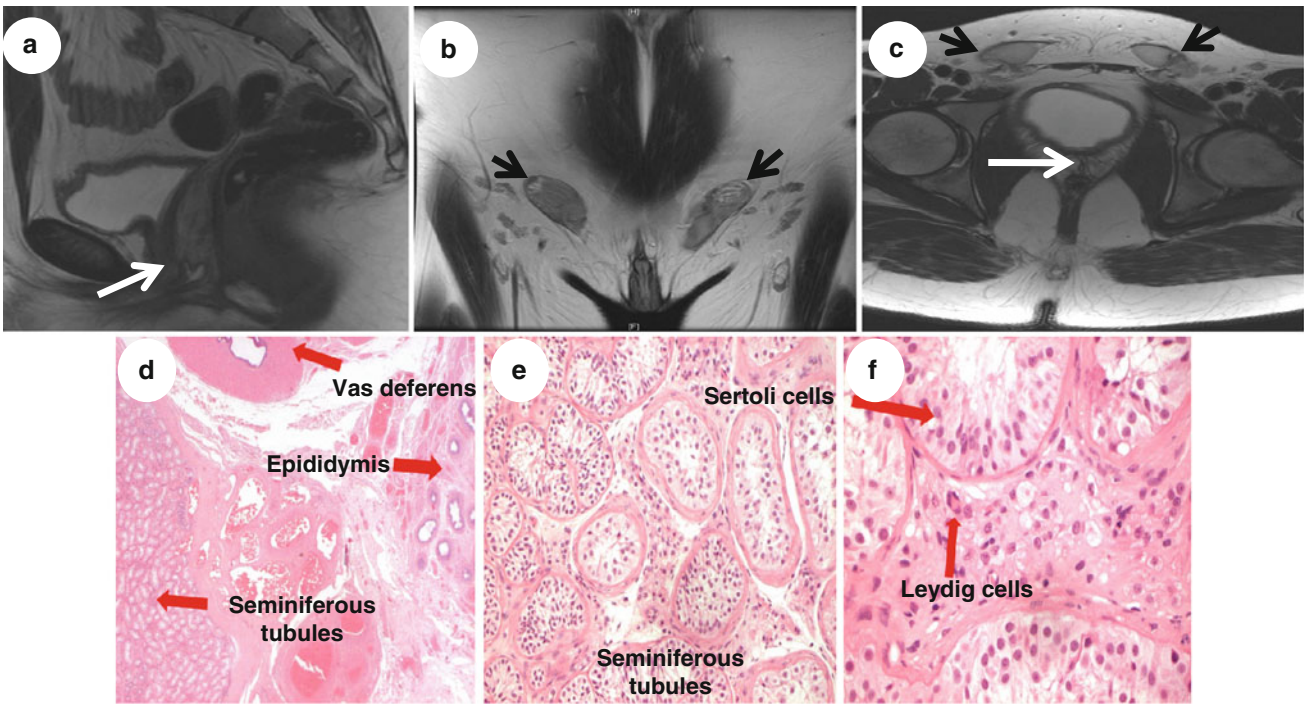

Fig. 1 **a** Sagittal, **b** Coronal and **c** Axial T2-weighted images of pelvis demonstrate an absent uterus and upper 2/3 of the vagina. Atrophy of the lower third of the vagina (*white arrows* **a, c**) is also seen. Both gonads are present and lie in the inguinal canals (*black arrows* **b, c**). **d–f** Sections through the gonadal tissue showing vas deferens, epididymis and rete testis in association with testicular tissue composed of seminiferous tubules (**d, e**) lined by Sertoli cells only (**f**). Interstitial Leydig cells (**f**) show cytoplasmic vacuolation

as a female due to a strong female gender identity and underwent gonadectomy. Bilateral testes were confirmed by histology (Fig. 1d–f). She remains on oestrogen replacement and is managed by a multidisciplinary DSD team, including psychological support.

The diagnosis of 5 alpha-reductase deficiency should be considered in a female with primary amenorrhoea and no breast development who is virilised with a high testosterone and a 46, XY karyotype [1]. Such a 46, XY DSD can also present in adulthood with an almost normal female phenotype with little or no virilisation [2]. It is an autosomal recessive condition due to mutations in the *SRD5A2* gene located on chromosome 2. Conversion of testosterone to the more active androgen, DHT, is impaired. DHT is critical in the male for development of the genital tubercle and folds to form the penis and scrotum, respectively. In its absence, the external genitalia may be ambiguous or female in appearance with only mild virilisation. Normal AMH production by Sertoli cells of the testis inhibits Mullerian duct development and hence lack of internal female genitalia. A USP is highly specific for 5 alpha-reductase deficiency [3], and was instrumental in finally establishing the cause of 46, XY DSD female in this family due to late presentation in the eldest sibling. This case highlights the importance of a multidisciplinary team with expertise across the spectrum of DSD [4]. An adult gender identity and role is a dynamic process and is variably dependent on multiple factors [5]. While DSD generally falls within the purview of the paediatrician, its presentation in adulthood adds a different complexity of management which warrants a holistic approach.

Acknowledgments The authors thank V. Pilford-Wilkie (Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge) for undertaking gene sequencing. The authors thank Dr. D. J. Halsall Department of Clinical Biochemistry for biochemical analysis, K. Mastroyannopoulou, Department of Paediatric Psychology and S. Kenwrick, Department of Clinical Genetics, East Anglian Medical Genetics Service.

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