CASE REPORT

Female phenotype with male karyotype: a clinical enigma

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SUMMARY

Development of gonadal and phenotypic sex during embryogenesis invariably corresponds to the genotypic sex. However, some disorders of sex development are associated with discordance between the chromosomal, gonadal or phenotypic sex which include complete androgen insensitivity syndrome, 46XY complete gonadal dysgenesis (Swyer syndrome) and, rarely, congenital adrenal hyperplasia due to CYP17A1 (17 α -hydroxylase) deficiency. The enzyme CYP17A1 includes 17 α -hydroxylase and 17,20-lyase which are required for the synthesis of cortisol and sex steroids, respectively. The consequent cortisol deficiency results in a compensatory increase in adrenocorticotrophic hormone (ACTH) drive, which stimulates the production of deoxycorticosterone and corticosterone leading to hypertension and hypokalaemia. Concurrent lack of sex steroids results in sexual infantilism without ambiguity. Both the genotypic males and females present during adolescence with a female phenotype, sexual infantilism and hypertension depending on the severity of the enzyme deficiency. We describe a case of CYP17A1 deficiency in a phenotypic female with 46XY karyotype who presented with sexual infantilism but without hypertension.

BACKGROUND

CYP17A1 deficiency occurs in <1% of all patients with congenital adrenal hyperplasia (CAH) and its estimated incidence is 1 in 50 000¹. It occurs due to the mutations in the gene CYP17A1, which is expressed in the adrenal gland and gonads and encodes the enzymes 17 α -hydroxylase and 17,20-lyase which are required for the synthesis of glucocorticoids and sex steroids, respectively. The characteristic presentation of this disorder is with delayed puberty in a typically phenotypic female irrespective of the karyotype. We report the case of a 14-year-old phenotypic female with 46XY karyotype who had hypergonadotropic hypogonadism and subclinical glucocorticoid deficiency due to CYP17A1 deficiency.

CASE PRESENTATION

A 14-year-old girl of Asian origin presented with complaints of sexual infantilism and primary amenorrhoea. She was the second child born out of a non-consanguineous marriage and was delivered preterm through normal vaginal delivery. There was no history of birth asphyxia, genital ambiguity at birth or salt crises in the neonatal period. She had normal developmental milestones but had

poor scholastic performance. On examination, she was noted to have a thin built with a height of 143 cm (midparental height=156 cm, target height=157.5 cm), height standard deviation score (SDS) - 3 and weight of 34 kg (body mass index=16.6 kg/m², weight SDS -2.6). She had neither breast development nor axillary or pubic hair (Tanner staging A-, P₁, B₁). Her external genitalia were unambiguously female (figure 1A and B). No inguinal or labioscrotal swellings or inguinal hernia were noted. Blood pressure was recorded to be normal (110–120/70–80 mm Hg) on multiple occasions. She had no skin or mucosal hyperpigmentation or postural fall in blood pressure. Ultrasound examination of the pelvis could not visualise any Müllerian structures but revealed a hypoechoic structure in the inguinal region bilaterally, which could possibly correspond to testicular tissue. Considering the patient's history and clinical signs, a hormonal profile (luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, 17 β -estradiol, dehydroepiandrosterone sulfate (DHEAS) measured by electro chemiluminescence immunoassay (ELECSYS-2010; Roche Diagnostics, Germany)) and karyotype analysis was ordered. The serum LH was 66.5 IU/L (normal range 7–8.6), FSH 118.5 IU/L (normal range 1.5–12.4), with undetectable testosterone (normal range 9.9–27.8), 17 β -estradiol 22.8 pmol/L (normal male range <74 pmol/L), and DHEAS 0.14 μ mol/L (normal range 0.66–6.67). Serum K⁺ was 4 mEq/L and there was no metabolic alkalosis. Her karyotype was 46XY. MRI of the pelvis revealed a hyperintense lesion measuring 1.2 $\times$ 1.0 $\times$ 0.8 cm on the right side and 1.1 $\times$ 1.0 $\times$ 0.5 cm on the left

Figure 1 (A) Absence of breast development in a phenotypic female aged 14 years. (B) Normal female genitalia in the same patient with absence of pubic hair.

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side in the inguinal region suggestive of hypoplastic testes. Other investigations included a 0800h cortisol 120 nmol/L (normal range 171–536) with a corresponding adrenocorticotrophic hormone (ACTH) value of 34.1 pmol/L (normal range 1.1–13.2). A 250 µg Synacthen stimulation test revealed a flat cortisol response (136.3 nmol/L) and 17 α -hydroxy progesterone concentration of 0.56 ng/mL. Serum progesterone concentration was markedly elevated (47.7 nmol/L, normal range <4.78). Testosterone and androstenedione showed a flat response to human chorionic gonadotropin (hCG) stimulation (2000 IU $\times$ 3 days) after 24 hours from the last injection (0.087 nmol/L and <0.3 ng/mL, respectively). Plasma aldosterone concentration was 6.3 ng/dL (normal range 1.0–16.0) with a plasma renin activity of 0.02 ng/mL/h (normal range 0.15–2.33). On psychosexual evaluation, the gender identity, role and behaviour of the patient were that of a female. Bone age was found to be delayed by 4 years on assessment using the modified Greulich-Pyle hand and wrist radiographic atlas. A diagnosis of 46XY disorder of sex development due to CAH 17 α -hydroxylase deficiency was made.

OUTCOME AND FOLLOW-UP

The patient underwent genitoscropy which revealed a blind vaginal pouch and was subsequently subjected to laparoscopic bilateral gonadectomy. The histopathological examination of the resected specimen revealed immature testes. The patient was initiated on hydrocortisone (10 mg/day in divided doses) and oestrogen (estradiol valerate 0.25 mg/day) replacement therapy. After 6 months of follow-up, her blood pressure was 110/70 mm Hg and she had Tanner staging A₁, P₂ and B₂. The dose of estradiol valerate was increased to 0.5 mg/day. Her gender role and behaviour were more strengthened to female sex after replacement therapies.

DISCUSSION

We described a case of CAH due to CYP17A1 deficiency in a phenotypic female with a male karyotype who presented with sexual infantilism but without hypertension.

Most of the cases of CAH are due to 21 α -hydroxylase deficiency (95%) and present during the neonatal period with ambiguous genitalia and/or salt crises. In contrast, rarer forms of CAH like CYP17A1 deficiency, which accounts for less than 1% of all cases of CAH, may remain undiagnosed as they neither have salt crisis nor genital ambiguity and usually present during childhood or adulthood.^{1,2}

The typical presentation of this enzyme defect is with sexual infantilism in a phenotypic female irrespective of the karyotype. These patients usually have hypergonadotropic hypogonadism with glucocorticoid deficiency along with hypertension and hypokalaemia. Mutations of the CYP17A1 gene located on chromosome 10q24.3 result in 17 α -hydroxylase deficiency. CYP17A1 catalyses both 17 α -hydroxylase and 17,20-lyase activity, which are quintessential for the synthesis of cortisol in the adrenal gland, and sex steroids in the adrenal gland and gonads, respectively.² Subjects with the 46XX karyotype and with CYP17A1 deficiency present with sexual infantilism and primary amenorrhoea due to the defect in gonadal steroid biosynthesis in spite of having Müllerian structures, while patients with the 46XY karyotype present with female external genitalia due to the absence of testosterone and dihydrotestosterone synthesis in the gonads and adrenal gland. Further, they do not have Müllerian structures because of the undisrupted anti-Müllerian hormone (AMH) production by the testes during embryogenesis,

thereby resulting in Müllerian duct regression. However, genital ambiguity may be present in few of these patients (46XY) who have partial enzyme insufficiency. LH and FSH are elevated due to the lack of negative feedback by the sex steroids. Our patient also presented during adolescence with delayed puberty due to hypergonadotropic hypogonadism and had female phenotype with 46XY karyotype.

Excessive ACTH secretion due to the enzymatic block in the cortisol biosynthesis pathway stimulates the production of progesterone, deoxycorticosterone (DOC) and corticosterone which are the steroid precursors proximal to the defect.³ The mineralocorticoid activity of DOC results in sodium retention, plasma volume expansion, hypertension and hypokalaemia which in turn inhibits the renin–angiotensin–aldosterone system and leads to decreased renin and low or normal aldosterone concentration as was also seen in our patient.¹ Approximately 90% of the patients are hypertensive at presentation; however, the absence of hypertension does not exclude the diagnosis. Sexual infantilism but absence of hypertension in the index patient can be explained by the differential levels of enzymatic activity of 17,20-lyase and 17 α -hydroxylase. The clinical consequences of cortisol deficiency in our patient were probably mitigated by the moderately elevated mineralocorticoids. The immediate precursor prior to the block, progesterone, is elevated and is a useful marker in the diagnosis of CAH due to CYP17A1 deficiency.⁴

In patients with isolated lyase deficiency, the 17 α -hydroxylation step is mostly preserved; hence there is no accumulation of DOC and, consequently, there is a lack of hypertension and hypokalaemia. Genotypic males with isolated lyase deficiency present with variable degrees of genital ambiguity and under-virilisation.¹

The differential diagnoses to be considered in a phenotypic female with a male karyotype include complete androgen insensitivity syndrome, 46XY complete gonadal dysgenesis (Swyer syndrome) and CAH due to CYP17A1 deficiency. The salient features of these disorders are listed in table 1. Other rare causes include StaR protein deficiency, CYP11A1 deficiency and Leydig cell hypoplasia due to LH G protein-coupled receptor mutation. Treatment comprises optimal glucocorticoid and sex hormone replacement. Glucocorticoids normalise the blood pressure and electrolytes by lowering the ACTH-driven mineralocorticoid excess.^{5,6} In rare cases, after initiating glucocorticoid therapy, patients may develop salt crises. It occurs as a consequence of decreased DOC production resulting from the inhibition of

Table 1 Differential diagnosis for female phenotype with male karyotype

Features	CAIS	46XY CGD	CYP17A1 deficiency	
			46 (XY)	46 (XX)
Phenotype	Female	Female	Female	Female
Hypertension	–	–	+	+
Müllerian structures	–	+	–	+
Gonadotropins	↑	↑	↑	↑
Sex steroids	↑	↓	↓	↓
Glucocorticoids	N	N	↓	↓
Mineralocorticoids	N	N	↑	↑

CAIS, complete androgen insensitivity syndrome; CGD, complete gonadal dysgenesis.

'+' and '–' stands for presence and absence of the condition, respectively.

Upward and downward arrows stand for high and low serum levels of respective hormones.

ACTH-driven adrenal steroidogenesis. Most of these patients regardless of their genotypic sex are reared as females except for a few patients with isolated lyase deficiency or partial CYP17A1 deficiency who have genital ambiguity and undervirilisation. After psychosexual evaluation, genotypic males may be subjected to gonadectomy and replaced with oestrogen. Genetic studies for CYP17A1 mutation are helpful in genetic counselling and

are required to establish the diagnosis where the clinical and biochemical profiles are discordant.

Contributors SS wrote the manuscript. PU investigated the patient and helped in the management of her case. SK was responsible for surgical management of the case. AB supervised the management of the case and edited the manuscript.

Competing interests None declared.

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Learning points

- ▶ Common causes of 46XY disorders of sex development with female phenotype are complete androgen insensitivity, complete gonadal dysgenesis and congenital adrenal hyperplasia (CAH) due to CYP17A1 deficiency.
- ▶ CAH due to CYP17A1 deficiency is rare but usually presents during adolescence with primary amenorrhoea and hypertension. However, the absence of hypertension does not exclude it.
- ▶ Hypergonadotropic hypogonadism, elevated deoxycorticosterone concentration and high serum progesterone confirm the diagnosis of CYP17A1 deficiency.
- ▶ Glucocorticoid replacement reduces the mineralocorticoid excess and normalises hypertension and hypokalaemia, while sex steroid replacement is required for the induction of puberty.

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