

Late presentation of simple virilising 21-hydroxylase deficiency in a Chinese woman with Turner's syndrome

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Classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency is a well-known disorder of sexual development (previously known as ambiguous genitalia) in genotypic female neonates. We report on a 66-year-old Chinese, brought up as male, with a simple virilising form of congenital adrenal hyperplasia associated with Turner's syndrome (karyotype 45,X/47,XXX/46,XX). His late presentation was recognised due to his exceptionally short stature and persistent sexual ambiguity. His condition was only brought to medical attention as he developed a huge abdominal mass, which later turned out to be a benign ovarian mucinous cyst. It is therefore important to look out for co-existing congenital adrenal hyperplasia in patients with Turner's syndrome and virilisation, after the presence of Y chromosome material has been excluded.

Case report

A 66-year-old Vietnam-born Chinese man was admitted to our department because of progressive abdominal swelling and bilateral ankle oedema for 1 year. On physical examination, he was noted to have a short stature with body height of 1.37 m. He had a normal complexion and no other dysmorphic features. His blood pressure was 99/55 mm Hg but with no postural drop. Abdominal examination revealed a distended abdomen without organomegaly or shifting dullness. Examination of his external genitalia revealed a micropenis with perineoscrotal hypospadias (Prader stage IV); no testes could be detected in/along both the scrotum and inguinal canals. However, he had male pattern of escutcheon, a beard, and no gynaecomastia. On further questioning, he reluctantly disclosed a history of urinary leakage since childhood and arrest of growth after puberty at the age of 10 years. Computed tomography of the abdomen revealed a 13.6 x 26.5 x 23.7 cm non-enhancing septated cystic mass arising from the retrovesical region.

Initial investigations revealed normal serum electrolytes and acid-base status. His renal function was impaired (serum creatinine of 172; reference range [RR], 62-126 $\mu\text{mol/L}$), and he had hypoalbuminaemia (serum albumin of 24; RR, 32-46 g/L). Baseline serum sex hormone profiles were as follows: testosterone at 9.2 (RR for male, 9.0-34.7) nmol/L, oestradiol at 176 (RR for male, 26-156) pmol/L, progesterone at 22.8 (RR for male, 0.7-4.3) nmol/L, luteinising hormone at 1.9 (RR, 1.7-8.6) IU/L, follicle-stimulating hormone at 3.0 (RR, 1.5-12.4) IU/L, androstenedione at 31.5 (RR, 0.8-3.1) nmol/L, and dehydroepiandrosterone sulfate at 11.6 (RR, 2.2-15.2) nmol/L. Tumour markers including beta-human chorionic gonadotropin, alpha-fetoprotein, carcinoembryonic antigen, and CA-125 were normal. A mosaic Turner karyotype with 10% monosomy X, 4% trisomy X, and 86% normal female karyotype was detected. The short synacthen test with 250 μg tetracosactrin was performed to unravel the possibility of congenital adrenal hyperplasia (CAH) with the following results: baseline adrenocorticotrophic hormone (ACTH) at 50.2 (RR, <10.1) pmol/L; baseline and 60-minute post-stimulation serum cortisol at 224 and at 260 nmol/L, respectively (reference level, >550 nmol/L post-stimulation); and baseline and 60-minute post-stimulation 17-hydroxyprogesterone (17-OHP) at 70 and 554 nmol/L, respectively (reference level of classical CAH, >300 nmol/L). Urinary steroid profiling (USP) by gas chromatography-mass spectrometry (GC-MS) showed grossly elevated metabolites of 17-OHP (Fig 1), including pregnanetriol, 17-hydroxypregnenolone and 11-oxo-pregnanetriol, compatible with 21-hydroxylase deficiency (21-OHD). Mutational analysis of the *CYP21A2* gene by multiplex ligation-dependent probe amplification and by polymerase chain reaction (PCR) followed by direct DNA sequencing showed deletion/conversion of the promoter to exon 4 in one allele and a hemizygous p.Ile172Asn mutation in the other allele. Using PCR no *SRY* gene could be amplified in the peripheral leukocytes and the surgical specimen (see below), which strongly reduced the possibility of hidden X/XY mosaicism or translocation of a Y-segment.

Key words

Adrenal hyperplasia, congenital; Steroids/urine; Turner syndrome; Virilism

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Hydrocortisone replacement was started and laparotomy was performed under steroid cover 8 months after the diagnosis. Apart from the large cystic mass which was later confirmed histologically to be a right ovarian mucinous cyst, findings during surgery included the left ovary, an atrophic uterus, and both fallopian tubes, all of which were then removed (Fig 2). No evidence of Wolffian structure could be identified. The postoperative course was uneventful and the diagnosis was disclosed to patient. The patient decided to continue perceiving himself as having a male gender with the possible need of testosterone replacement. Further family screening for CAH and the possibility of parental consanguinity could not be delineated because the patient was an orphan.

一名特納氏綜合徵華籍女性患者的單純雄性化型21-羥化酶缺乏症的遲診病例

因21-羥化酶缺乏症而有先天性腎上腺皮質增生症在基因型女嬰身上是一個已知的性發育障礙（曾被稱為曖昧生殖器）。本文報告一名66歲一向是男性身份的華籍病人，他出現與特納氏綜合徵有關的先天性腎上腺皮質增生症的單純雄性化型（染色體核型45,X/47,XXX/46,XX）。由於病人身材特別矮小，性器官也很模糊，所以很遲才發現這病症，而他也因為腹部有巨大腫瘤，後被證實為良性的卵巢粘液性囊腫才被確診此症。如果病人有特納氏綜合徵及雄性化型，當證實無Y染色體後，便應替病人檢查是否患有先天性腎上腺皮質增生症。

Discussion

We report a case of simple virilising form of CAH due to 21-OHD in a 66-year-old Chinese subject with a mosaic Turner karyotype. This condition is one of the most common autosomal recessive disorders of impaired cortisol biosynthesis. As a result of 21-OHD, adrenal synthesis of cortisol and in most cases also that of aldosterone is impaired. The consequential increased secretion of ACTH leads to adrenal hyperplasia and accumulation of cortisol precursors that are diverted to androgen production. Depending on the degree of enzyme deficiency,

the CAH genotype can have several phenotypes. One is a salt-wasting type with a potential for a life-threatening salt-wasting crisis during the neonatal period in addition to prenatal virilisation in females. The other phenotype is a simple virilising type with prenatal or postnatal virilisation in females or pseudoprecocious puberty in males. Also there is a non-classical type with pseudoprecocious puberty, hirsutism, acne, and subfertility in females.¹ Disease severity correlates with *CYP21A2* allelic variation, located on chromosome 6, with an 80 to 90% genotype-phenotype correlation.² The prevalence of classical 21-OHD has been reported to be 1:10 000

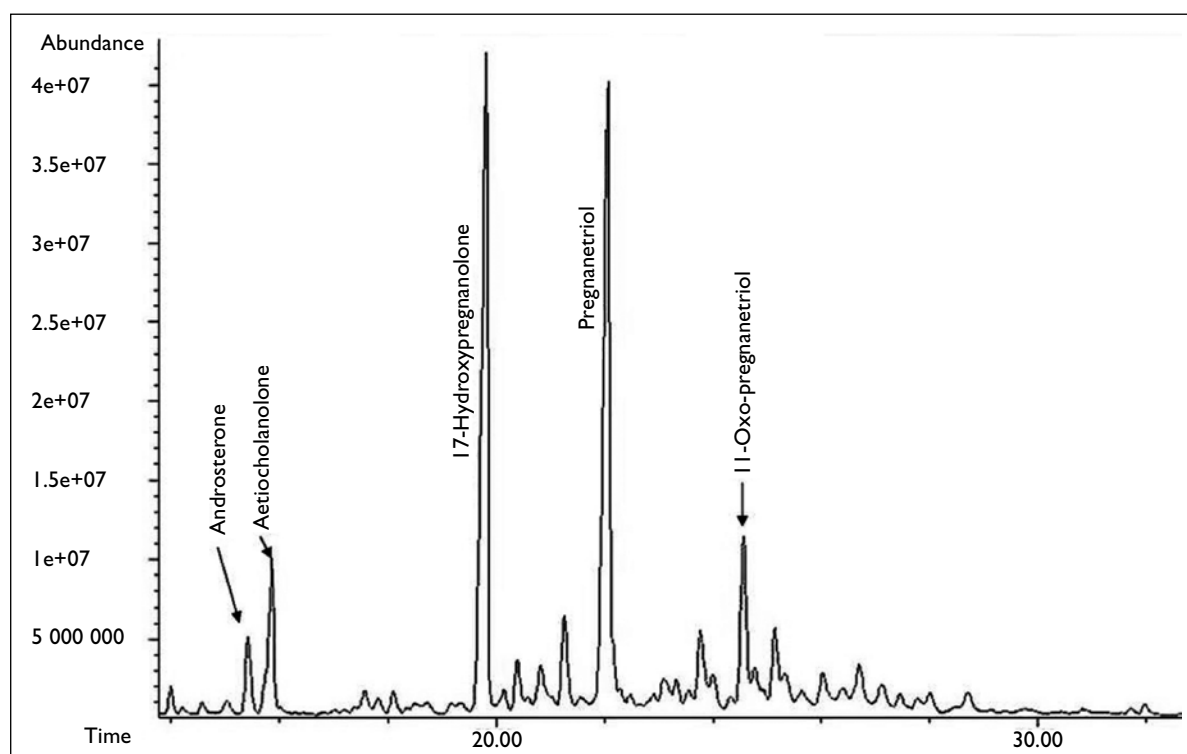


FIG 1. Urinary steroid profiling showing grossly elevated metabolites of 17-OHP (17-hydroxypregnenolone, pregnanetriol and 11-oxo-pregnanetriol) and androgen (androsterone and aetiocholanolone), which are characteristically found in patients with 21-hydroxylase deficiency

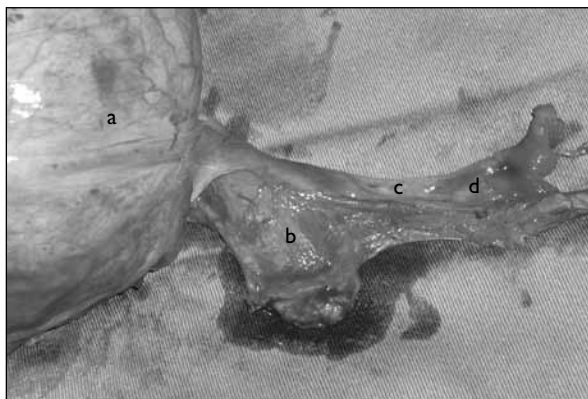


FIG 2. Gross specimen showing (a) the huge (19 x 23 x 8 cm) right ovarian mucinous cyst, (b) atrophic uterus, (c) left fallopian tube, and (d) left ovary in a 66-year-old phenotypic Chinese male with 21-hydroxylase deficiency and Turner's syndrome

to 1:18 000 inhabitants with a wide ethnic variation, while the non-classical 21-OHD is more prevalent and occurs in 0.1 to 2% of the general population.¹

Turner's syndrome (TS) has an estimated point prevalence of 1 in 2500 to 1 in 3000 live-born phenotypic females, and is characterised by short stature, primary gonadal failure, and a wide spectrum of clinical features.³ There is also a wide range of karyotypes, in which half of them have the classical monosomy X (45,X) and others have various mosaicism for 45,X. Virilisation occurring in patients with TS should prompt a search for the Y-chromosome-bearing cell line, as they are at risk of developing malignant gonadal tumours. If the existence of Y chromosome material cannot be identified by cytogenetic or molecular analysis, the rare occurrence of co-existing CAH should be looked for to account for virilisation and/or sexual ambiguity.

So far, only six cases with both TS and CAH have been reported in the literature.^{4,9} Except for one case⁴ presenting with diminished endometrial receptivity during in-vitro fertilisation in a 28-year-old woman, they all presented with different degrees of virilisation in phenotypic females. All except one case had a mosaic Turner karyotype.⁵ The age of presentation varied from 1 to 28 years, depending on the degree of 21-OHD. The 1-year-old Caucasian girl presented with disordered sexual development and moderate salt-wasting episodes early in the neonatal period.⁶ She was diagnosed to have mosaic Turner karyotype with 45,X/46,XX (5:11) and 21-OHD with elevated 17-OHP, androstenedione, and testosterone. Another case was a 23-year-old woman who presented with primary amenorrhoea, a phallus 3 cm in length, a urogenital sinus, and a 45,X/46XX karyotype.⁷ The remaining two cases presented with clitoromegaly and mosaic TS in an 8-year-old⁸ as well as a 5-year-old girl.⁹ Our patient had the most advanced type of virilisation (Prader stage IV) and the latest presentation which might have been

related to his reluctance in seeking medical care and the absence of salt-wasting episodes. Were it not due to the huge ovarian cyst, his intriguing medical condition might never have been exposed. In fact, the development of a large ovarian cyst in a 22-year-old Japanese woman with 21-OHD has already been reported.¹⁰ In that case, the 8.5 x 6.2 cm ovarian cyst disappeared once hyperandrogenism was controlled with glucocorticoid therapy adjustment, and it was postulated that prolonged hyperandrogenism may have contributed to its development.¹⁰ Another distinctive feature of our patient was his exceptionally short stature. The final body heights of patients with untreated mosaic TS and Y chromosome material are usually higher.³

It is difficult to diagnose co-existing CAH, particularly the non-classical type, in patients with TS, as typical signs such as short stature, menstrual irregularities, primary infertility, and hirsutism may be present in both diseases. Therefore, it is important to measure 17-OHP levels in patients with TS, especially in the presence of moderate-to-severe hirsutism or virilisation. Although basal or ACTH-stimulated 17-OHP levels in patients with TS may only overlap with that of heterozygous 21-OHD patients,¹¹ 17-OHP levels of our patient (particularly the stimulated level) clearly fell into the diagnostic range of classic CAH.¹ If 17-OHP values are non-diagnostic, the importance USP by GC-MS and mutational analysis to confirm CAH in patients with TS cannot be overemphasised. Apart from its significance in gender assignment and appropriate reconstructive surgery, early diagnosis of co-existing CAH is also important for proper management of growth failure; unopposed hyperandrogenism may lead to initial skeletal maturation which masks the growth disorder. However, premature closure of growth plates leads to short final heights, as seen in our patient.

More than 100 *CYP21A2* mutations have been reported.¹² Mutational analysis in our patient revealed gross deletion/conversion of the promoter to exon 4 in one allele and hemizygous p.Ile172Asn mutation in the other allele. The former accounted for 27% and the latter 16% of all the mutations detected in 35 Chinese patients in a local study.¹³ The missense mutation p.Ile172Asn is known to retain 1 to 2% of normal 21-hydroxylase activity and results in simple virilising CAH, compatible with the phenotype of our patient.

Conclusion

We have reported a case of mosaic TS and simple virilising form of CAH, who presented with a huge ovarian cyst. Although it is rare, co-existing CAH should be suspected in patients with TS and various degrees of virilisation, after the presence of Y chromosome material has been ruled out.

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Answers to CME Programme

Hong Kong Medical Journal April 2013 issue

Hong Kong Med J 2013;19:150-5

I. Eyelid tumours and pseudotumours in Hong Kong: a ten-year experience

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|---|---------|----------|----------|----------|----------|
| A | 1. True | 2. False | 3. True | 4. False | 5. False |
| B | 1. True | 2. True | 3. False | 4. False | 5. True |

Hong Kong Med J 2013;19:159-67

II. Brugada syndrome

- | | | | | | |
|---|----------|----------|----------|----------|---------|
| A | 1. True | 2. False | 3. False | 4. True | 5. True |
| B | 1. False | 2. True | 3. False | 4. False | 5. True |