CASE REPORT

A Young Woman with Hypogonadism, Hypertension and Hypokalaemia

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SUMMARY

We report a case of a 16 years old girl who presented sequentially with primary amenorrhoea, hypertension and hypokalaemia. Eight years later, she was finally diagnosed with 17alpha-hydroxylase deficiency congenital adrenal hyperplasia. Previous antihypertensive medications were stopped. Hydrocortisone alone successfully maintained normotension and normokalaemia.

KEY WORDS:
Congenital Adrenal Hyperplasia, 17-alpha hydroxylase deficiency, Hypertension, Hypokalaemia, Hypogonadism

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders resulting from various genetic defects in the enzymes involved in cortisol biosynthesis. The clinical manifestations of the different disorders differ according to the site of block, accumulation of upstream steroids and deficiency of downstream steroids [1].

11-beta hydroxylase (CYP11B1) deficiency and 17-alpha hydroxylase (CYP17) deficiency are two forms of hypertensive CAH; the former causes virilization whereas the latter pubertal failure. 17-alpha hydroxylase deficiency (17-OHD) has an estimated incidence of about 1:50,000 newborns and roughly 1% of all cases of CAH [2].

We report herewith a case of 17-OHD in a 24 years old girl whose diagnosis was delayed for eight years.

CASE REPORT

Miss CYF was 16 years old when she presented to the gynaecologist with primary amenorrhea in 1999. She had normal external female genitalia but absent secondary sexual characteristics. Initial investigations were suggestive of primary ovarian failure: FSH 63.2 uIU/ml (1.7-9.3 uIU/ml), LH 37.5mIU/ml (0.9-9.3 uIU/ml), Estradiol 32.7 pg/ml (follicular: 24-138 pg/ml; luteal: 19-164 pg/ml; periovulatory 107-402 pg/ml; postmenopausal: < 36 pg/ml). Her karyotype was 46, XX. Ultrasound pelvis showed a small atrophic uterus and no ovary visualized. She was treated with Progyluton (estradiol valerate/norgestrol) by the gynaecologist to induce monthly withdrawal bleed. There was no improvement in her secondary sexual characteristics.

She developed hypokalaemic hypertension in 2002 with blood pressure of 150/110mmHg and potassium of 3.4 mmol/l (3.5 – 4.5 mmol/l)). Computed Tomography of abdomen showed normal adrenal glands. She was started on Atenolol 50mg od, but subsequently changed to Amlodipine 5mg daily (later increased to 10 mg daily) as she was intolerant to atenolol. Spironolactone 50mg bd was added as potassium-sparing agent in view of persistent hypokalaemia (K ~ 2.6mmol/L) despite supplementation with potassium chloride 1200mg bd. Her blood pressure improved to 120-130/80-90mmHg.

She worked as an accounts clerk with a private company after obtaining her diploma in accountancy. Her parent's marriage was non-consanguineous and there was no family history of similar condition among three other siblings (a younger brother and two younger sisters).

An endocrine evaluation was sought in 2007. She was not pigmented. Her blood pressure (BP) was 127/75mmHg, weight 55.5kg, height 168cm, BMI = 19.7 and arm span 167cm. There was no Marfanoid features. Her breasts and genitalia were both prepubertal (Tanner Stage 1). Major systems examinations were unremarkable.

Further investigations were done after stopping Progyluton and spironolactone for six weeks (Figure 1): FSH 76.4 U/L (1.7-9.3 U/L), LH 52.2 U/L (0.9-9.3 U/L), estradiol 49 pmol/l (103-632 pmol/l), progesterone 12.0 nmol/l (1.2-3.7 nmol/l), testosterone 0.7 nmol/l (0.5-2.6 nmol/l), ACTH 46 mIU/L (<46), aldosterone 280 pmol/l (100-860 pmol/l seated), renin 7.5 uIU/ml (7 to 50 uIU/ml). Her cortisol response to ACTH was suboptimal [<5.50 nmol/l at 0 minute, 17.52 nmol/l at 30 minutes, 16.71 nmol/l at 60 minutes (normal response >550 nmol/l at 60 minutes)]. 17-OH progesterone was low and did not respond to ACTH [1.1 nmol/l at 0 minute, 1.3 nmol/l at 30 minutes, 1.1 nmol/l at 60 minutes (normal response < 30 nmol/l)].

The above biochemistry, in conjunction with her clinical features, was consistent with a diagnosis of 17-OHD CAH, particularly the low androgen and estradiol levels and the raised FSH, LH and progesterone. Aldosterone was normal but renin was low, suppressed by the presence of other mineralocorticoids (such as 11- deoxycorticosterone (DOC) and corticosterone (B)) which were not measured. Genetic testing was unavailable, but was also deemed unnecessary in view of the classical presentation.

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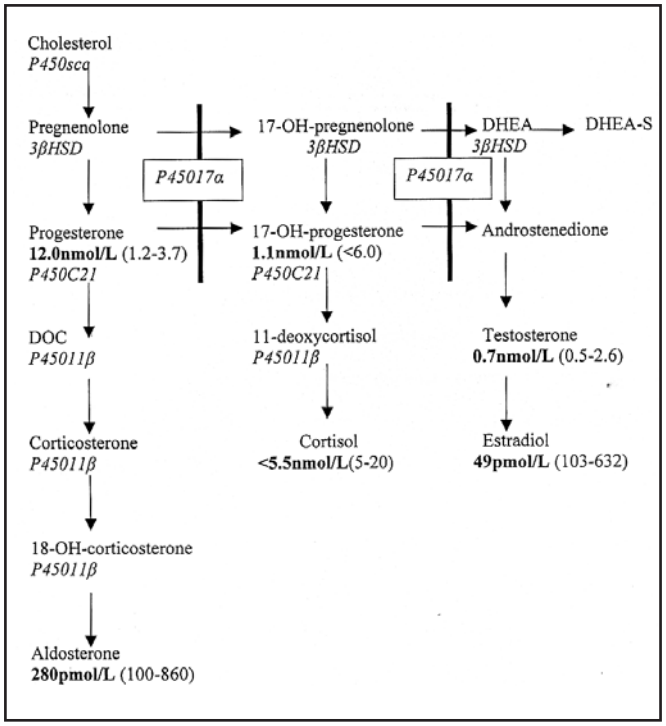

Fig. 1: Steroidogenic pathways in the adrenal cortex and gonads. Patient's plasma levels and normal values (in parentheses) are shown. P450scc, cholesterol side chain cleavage cytochrome P450; P45017α, 17α-hydroxylase cytochrome P450; P450C21, 21-hydroxylase cytochrome P450; P45011β, 11β-hydroxylase cytochrome P450; 3β-HSD, 3β-hydroxysteroid dehydrogenase; DOC, deoxycorticosterone; DHEA, dehydroepiandrosterone; DHEA-S, DHEA-sulfate.

She was initially treated with Hydrocortisone 10mg morning, 5mg lunchtime, 5mg evening, Amlodipine 10mg od, Slow K 2 tabs bd and Progyluton. Steroid Medic-Alert card was issued and patient was taught how to manage her steroid dose during stress and illness.

Potassium supplement was successfully stopped after one month of steroid replacement and Amlodipine weaned off about eight months after. During her last review, she was well with BP of 110/71mmHg, serum potassium 4.7mmol/l on Hydrocortisone 10mg am, 5mg pm and Progyluton.

DISCUSSION

The commonest cause of CAH is 21-hydroxylase deficiency [1,3], and the second commonest appears to be lipoid CAH in Japan and Korea, 11-hydroxylase deficiency in Middle East and 17-OHD in Brazil [3]. The clustering of CAHs in certain ethnic populations is thought to be due to founder effects, suggesting a high coefficient of inbreeding that account for over 80 percent of mutant alleles, although consanguinity may not be consistently reported [3].

Almost 45 mutations have been described for CYP17 gene which encodes P450c17 enzyme that has both 17alpha-hydroxylase and 17, 20-lyase activities [2]. About 150 cases of 17-OHD CAH have been reported[4]. Deficient 17 alpha-hydroxylation of pregnenolone and progesterone and subsequent absence of sex steroids in the adrenal glands and gonads cause hypogonadism and sexual infantilism [3]. There is considerable variation in the menstruation capacity in 46XX females and degree of genital virilization in 46XY males [4]. The accumulation of upstream mineralocorticosteroids [17 deoxysteroids 11–deoxycorticosterone (DOC) and corticosterone (B)] cause low-renin hypertension and hypokalemia (Figure 1). There is also wide variation in the age of onset of hypertension, degree of hypokalaemia and aldosterone levels [3].

Typical laboratory findings include increased basal progesterone, and reduced cortisol, 11-deoxycortisol and 17-alpha-hydroxyprogesterone levels. Likewise, deficiency of 17,20-lyase cause a reduction in dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone and estradio[1]. Due to negative feedback of the latter two sex hormones, FSH and LH are increased. ACTH is generally increased due to hypocortisolism but high corticosterone levels provide adequate glucocorticoid cover and prevent symptoms of hypocortisolism [4].

The aim of treatment is to suppress the ACTH drive to overstimulate mineralocorticoids, and provide physiological glucocorticoid replacement while preventing iatrogenic Cushing's syndrome. Individual treatment response in terms of BP control can be variable. At puberty, female patients should be given estrogen together with progesterone.

In conclusion, we presented a genetically Chinese female whose diagnosis of 17-OHD CAH was delayed for eight years due to misdiagnosis of primary ovarian failure when she presented with primary amenorrhoea. Detection of hypertension three years later prompted an, albeit delayed, endocrinology referral which led to the final diagnosis of 17-OHD CAH. Treatment with hydrocortisone cured her hypertension and hypokalaemia. She remained on oral contraceptive pills. We recommend a high index of suspicion for secondary hypertension in particular CAH in young female patients who present with primary amenorrhea or hypogonadism, hypertension and hypokalamia.

REFERENCES

1. www.uptodate.com/online/content/topic.do?topicKey=adrenal/12879&selectedTitle=7~84&source=search_result. Uncommon Causes of Congenital Adrenal Hyperplasia Accessed 28 April 2009.
2. Brooke AM, Taylor NF, Shepherd JH *et al.* A Novel Point Mutation in P450c17 (CYP17) Causing Combined 17α-hydroxylase/ 17, 20-Lyase deficiency, J Clin Endocrinol Metab 2006; 91(6): 2428 - 31.
3. Costa-Santos M, Kater CE, Auchus RJ *et al.* Two prevalent CYP17 Mutations and Genotype-Phenotype Correlations in 24 Brazilian patients with 17-Hydroxylase Deficiency. J Clin Endocrinol Metab 2004; 89(1): 49 - 60.
4. Wei JQ, Wei JL, Li WC *et al.* Genotyping of 5 Chinese patients with 17·-hydroxylase deficiency diagnosed through high-performance liquid chromatography serum adrenal profile: Identification of two novel CYP17 mutations. J Clin Endocrinol Metab 2006; 91(9): 3647 - 53.