Journal of Pakistan Association of Dermatologists. 2018; **28 (2)**: 262-265

Case Report

Female pseudohermaphroditism: Congenital adrenal hyperplasia presenting with diffuse hyperpigmentation

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Abstract The term congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both. The clinical presentation varies according to chromosomal sex. The sex of neonate with CAH is often initially unclear because of genital ambiguity. We report a case of 25-year-old phenotypically male, presenting with generalized hyperpigmentation for 5 years and occasional syncope for 1 year. On examination there were sparse axillary and pubic hair with ambiguous genitalia. 46XX karyotype, hypoplastic uterus on CT scan and elevated ACTH and 17-hydroxyprogesterone levels lead to the diagnosis of female pseudohermaphroditism due to congenital adrenal hyperplasia and patient was started on glucocorticoids and fludrocortisone by endocrinologist and was also referred to plastic surgeon.

Key words
Pseudohermaphroditism, congenital adrenal hyperplasia, androgens.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition with an incidence of approximately 1 in 12,500 Caucasian births.[1] It is caused by the mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis).[2] Most of these conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected infants, children or adults.[3] CAH is characterized by deficiency of one of the enzymes required to make cortisol - required for stress response, maintenance of blood pressure; aldosterone - required for salt retention; or androgens - for virilization of the fetus (rare form).

CAH is the most common cause of female pseudohermaphroditism. It can rarely be a result of virilizing adrenocortical tumours.[4] Approximately 95% of cases of CAH are due to deficiency of enzymes 21-hydroxylase (21-OH) which catalyzes the conversion of progesterone and 17-hydroxyprogesterone (17-OXP) to deoxy-corticosterone and 11 deoxy-cortisol respectively.[1,3,4]

Clinical features of CAH vary depending upon the form of CAH and the sex of patient. Due to excess androgens there may be precocious puberty or failure of puberty to occur (sexual infantilism: absent or delayed puberty); ambiguous genitalia, in some females, such that it can be initially difficult to identify external genitalia as ‘male’ or ‘female’; early pubic hair and rapid growth in childhood; excessive facial hair, virilization and/or menstrual irregularity in

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adolescence; infertility due to anovulation; functional and average sized penis in cases involving extreme virilization (but no sperm), enlarged clitoris and shallow vagina; and pigmentation (due to raised ACTH with lack of cortisol). Inadequate mineralocorticoids may lead to vomiting due to salt-wasting leading to dehydration and death.[5]

In this report, we present a case of CAH presenting in skin OPD with diffuse hyperpigmentation.

Case Report

A 25-year-old, phenotypically male, presented with generalized diffuse hyperpigmentation with accentuation at exposed body parts and major flexures for the last 5 years. He had occasional history of syncope for the last 1 year. There was no history of fever, weight loss, vomiting or any drug intake. He was born to non-consanguineous parents after an uneventful full term vaginal delivery. The patient had a body weight of 43kg and height of 4.6ft. On examination, patient had diffuse hyperpigmentation with accentuation at face, hands and feet, axillae, groin, genital area, knuckles, elbows, knees, nipples, areola and appendectomy scar mark (**Figure 1** and **2**).

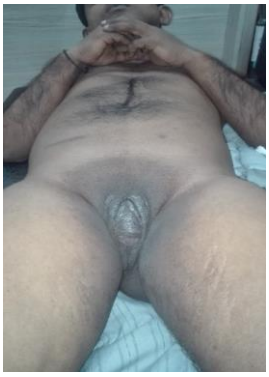
Hyperpigmentation of labial, gingival, buccal mucosae and dorsal surface of tongue also noted **(Figure 3** and **4**). Nails showed hyperpigmented longitudinal bands. There were sparse axillary and public hair with ambiguous genitalia, absent scrotum, incompletely developed penile urethra, partially developed bilateral labia and gynecoid pelvis. He had sitting blood pressure of 120/80mmHg, with an asymptomatic postural drop of 20mmHg on standing.

The biochemical evaluation revealed fasting glucose 64mg/dl, Na^+140 mmol/L, K^+3.90 mmol/L, Cl^-102mmol/L. His complete blood count, renal and liver function tests and viral markers (HbsAg, anti-HCV antibodies) were normal.

Cytogenetic analysis showed 46XX **(Figure 5)**, whereas abdominopelvic ultrasound revealed a hypoplastic uterus (30x27x15mm) with normal endometrial cavity; no ovaries, seminal vesicle and prostatic tissue were demonstrated. CT abdomen and pelvis showed hypoplastic uterus posterior to bladder and bilateral adrenal hyperplasia in the form of dense elongated mass, with central calcification, measuring 5.9x5.1x3.7cm and 5.0x1.7x1cm on right and left suprarenal area, respectively **(Figure 6)**. Tiny ovaries and bilateral empty scrotal sac were present. No prostate was seen.

The endocrinological analysis revealed serum cortisol 8.98 µg/dl, elevated ACTH (16.0pg/ml), raised testosterone level (18.5ng/ml), markedly elevated serum 17-hydroxyprogesterone (>20ng/ml), estrogen 140pg/ml, progesterone 4209ng/dl, FSH 0.05mIU/ml, and LH 0.05 mIU/ml. Short synacthen test showed cortisol levels of 129 nmol/L, 134 nmol/L and 151 nmol/L at 0 minutes, 30 minutes and 60 minutes, respectively.

The clinical findings and investigations suggested the diagnosis of female pseudohermaphroditism due to congenital adrenal hyperplasia resulting in adrenogenital syndrome. The patient was started on glucocorticoid and fludrocortisone replacement by an endocrinologist with a plan to follow-up.



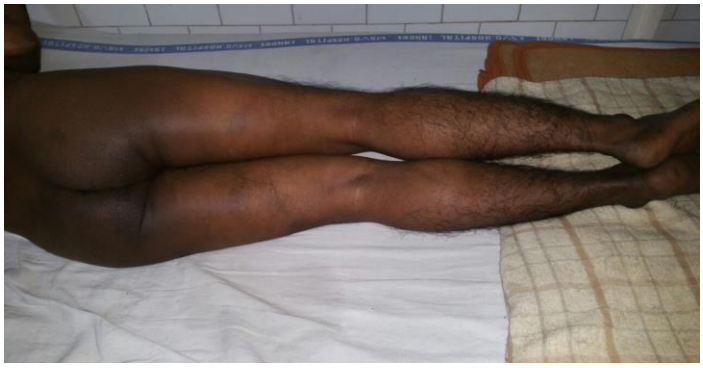
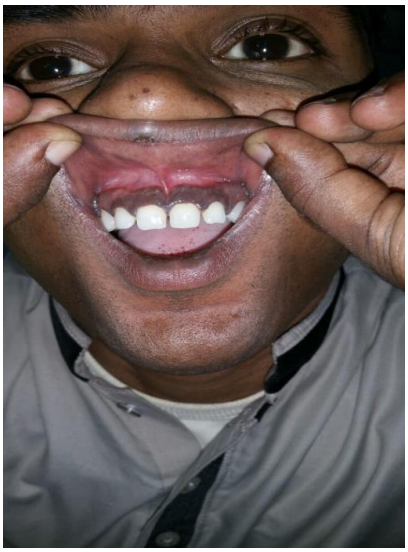


Figure 1, 2 showing ambiguous genitalia, absent scrotum, partially developed penile urethra, hyperpigmentation of face, groins and buttocks, respectively.



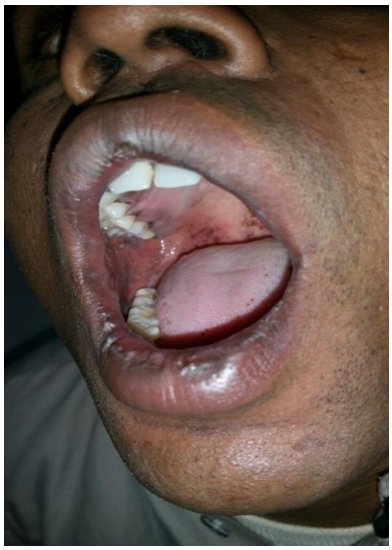


Figure 3, 4 showing hyperpigmentation of labial, gingival and buccal mucosae.

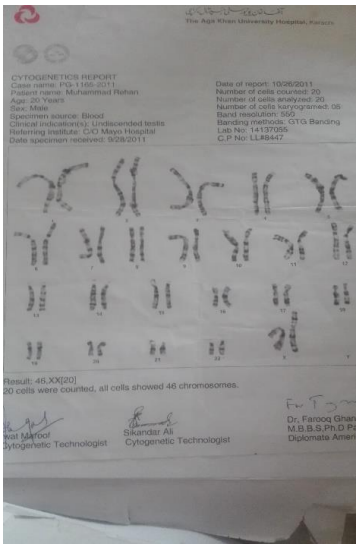


Figure 5 Cytogenetic analysis showing 46XX.

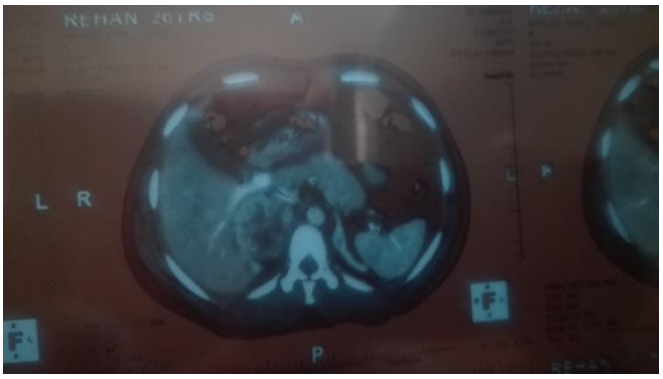


Figure 6 CT scan showed hypoplastic uterus, bilateral adrenal hyperplasia in the form of dense elongated mass with calcification.

Discussion

Excessive androgen levels in the female may affect primary sexual characteristics by masculinizing the fetal external genitalia to produce female pseudohermaphroditism or secondary sexual characteristics by inducing changes similar to those characteristic of male

puberty to produce virilization. Therefore, female pseudohermaphroditism is a condition in which the gonadal sex is female, but the external genitalia are masculinized. CAH due to 21-hydroxylase deficiency is the most common cause of ambiguous genitalia in genotypically normal female infants (46XX). Males with classic CAH generally have no signs of CAH at birth. Age of diagnosis of males with CAH varies and depends on the severity of aldosterone deficiency.[5,6]

Cortisol is an adrenal steroid hormone, essential for normal endocrine function. Deficient cortisol production is a hallmark of most forms of CAH. Inefficient production of cortisol results in rising levels of ACTH because of negative feedback. This increased ACTH induces overgrowth (hyperplasia) and overactivity of steroid producing cells in adrenal cortex.[6,7]

Cortisol deficiency in CAH is usually partial and not a very serious problem for these patients. The resulting excessive or deficient production of other classes of hormones, for the synthesis of which cortisol plays an important part, produces the most important problems for patients with CAH.[8]

The fundamental aim of endocrine therapy for CAH is to provide replacement of the deficient hormones. Glucocorticoid administration both replaces the deficient cortisol and suppresses ACTH over production, leading to reduced production of other adrenal steroids and amelioration of their noxious effects, averting further virilization, slowing accelerated growth and bone age advancement to a more normal rate and allowing a normal onset of puberty. Hydrocortisone (cortisol) in oral form is the preferred and usual mode of treatment. Patients with classic 21-hydroxylase deficiency and salt wasting require mineralocorticoid replacement. The cortisol analog 9α-fluorohydrocortisone (Florinef®) is used for its potent mineralocorticoid activity.[8,9]

Intersex management is the most important part. This is a critical aspect of treatment, because the decision of sex assignment has obvious lifelong implications.[9,10]

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