

## CASE REPORT

# Primary ammenorrhoea due to hyperandrogenism arising from a recessive genetic disorder (Non Classical Congenital adrenal hyperplasia)– a rare association

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### ABSTRACT

Androgen excess either from adrenal or ovarian origin or due to excessive peripheral conversion leads to hirsutism and virilization. We are describing a case who presented with a rare combination of hyperandrogenism and primary amenorrhea due to non-salt wasting congenital adrenal hyperplasia. The patient presented with severe hyperandrogenism (hirsutism, masculinization and clitoromegaly) in peri pubertal period. Investigations revealed a moderate hyperandrogenism in non-tumor range (testosterone < 2 ng/ml) with no identifiable lesion in adrenal or ovaries. We conclude that while evaluating a case of primary amenorrhea NCAH should be considered as one of the differential diagnoses, particularly in our community where consanguinity is prevalent. [IJEM 2007;11(1&2):57-59]

*Key Words*: Hyperandrogenism, primary ammenorrhoea, NCAH, hirsutism

### INTRODUCTION

Androgen excess either from adrenal or ovarian origin or due to excessive peripheral conversion leads to hirsutism and virilization(1). Mild androgen excess characterized by hirsutism (usual score < 16); acne vulgaris, oligo or anovulation is caused by non-neoplastic (i.e. functional) adrenal or ovarian androgen hypersecretion like polycystic ovary syndrome (PCOS), non-classical adrenal hyperplasia (NCAH) etc(2). Severe hyperandrogenism usually due to adrenal or ovarian neoplasm, iatrogenic or factitious androgen use or rarely congenital adrenal hyperplasia can manifest with defeminization (breast regression, amenorrhea > 6 months) and virilization (masculine body habitus, voice changes, clitoromegaly and severe, cystic acne)(3). We are presenting a case who presented with a rare combination of hyperandrogenism and primary amenorrhea due to non-salt wasting congenital adrenal hyperplasia.

### Case Report

T.G., 18 year female born of full term normal delivery with uneventful postnatal and early development and

insignificant family history was brought to our clinic with 8 years history of coarsening of voice, generalized male-pattern hair growth, non development of breasts and failure to achieve menarche. She however, had history of two episodes of vaginal bleeding with prednisolone but not with progesterone replacement. She gave no history of genital ambiguity at birth, history of protracted diarrhea, hypertension or salt craving. Clinical examination revealed a masculine habitus, male voice, acne vulgaris, moderate hirsutism (Ferriman-Gallway score > 20) and mild hyper-pigmentation. She was normotensive and systemic examination was unremarkable. Anthropometric assessment showed a height of 156 cm (75-90th percentile) with midparent height of 157 cm (75-90th percentile) upper segment of 75 cm, lower segment of 81 cm, arm span of 165 cm and weight of 57 kgs (>90th percentile) Sexual maturity rating revealed, a small breast (Tanner stage I) and normal pubic hair (Tanner IV) development. Genital examination showed female genitalia with mild clitoromegaly.

Laboratory data revealed normal blood counts, liver and kidney functions, urinalysis, plasma lipids, electrolytes, electrocardiography and chest roentgenography. Bone age maturation was appropriate i.e. 18 + 2 years (TW2 method) Endocrine work up indicated normal T4, TSH, LH, FSH and prolactin but serum cortisol was low. (Table 1a). Basal testosterone and

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17-OHP were elevated but were suppressible with dexamethasone (Table 1b). USG and CECT abdomen showed bilateral hyperplastic adrenal glands with small uterus (5.4 cm X 2.2 cm x 1.42 cm) and cystic ovaries on both sides, with ovarian volume measuring = 8.8 ml in R and = 5.0 ml in L side).

**Table 1a. Endocrine profile of the patient**

Hormone	T4	TSH	LH	FSH	PrI
Observed value	98	3.2	8.3	5.7	8.0
Normal range	nmol/L	IU/ml	IU/ml	IU/ml	ng/dl

**Table 1b. Dexamethasone suppression test**

Hormone		Testosterone	17OHP	Cortisol
Basal		1.5	>20	5.0
Post Dexamethasone	3rd day	0.25	5.6	-
	7th day	0.12	2.5	3.6
Normal range (units)		0.3-0.70	0.28-4.0	5-25
		ng/ml	ng/ml	mg/ml

## DISCUSSION

Congenital adrenal hyperplasia results from an autosomal recessive defect in the activity of one of the steroidogenic enzymes necessary for corticosteroid hormone synthesis by the adrenal gland. Because of the defective enzymes, the adrenal is unable to secrete requisite quantities of glucocorticoids (mainly cortisol) or mineralocorticoids (mainly aldosterone), each enzyme deficiency can lead to clinical and biochemical syndromes (4). Virilizing CAH can be as a result of 21-OH, 3 $\beta$ -HSD or 11-bOH deficiency. Nonclassical congenital adrenal hyperplasia (CAH) owing to steroid 21-hydroxylase deficiency (NC21OHD) is the most frequent of all autosomal recessive genetic diseases, occurring in one in 100 persons in the heterogeneous New York City population. NC21OHD occurs with increased frequency in certain ethnic groups, such as Ashkenazi Jews, in whom one in 27 express the disease (5). NC21OHD is under diagnosed in both male and female patients with hyperandrogenic symptoms because hormonal abnormalities in NC21OHD are only mild to moderate, not severe as in the classical form of CAH. Unlike classical CAH, NC21OHD is not associated with ambiguous genitalia of the newborn female (6). The pathogenic mechanism is that the defect in one of the enzymes leading to failure of negative feed back causing very high ACTH levels. This causes hyper-stimulation of adrenal glands with accumulation of precursors proximal to the defect accompanied by insufficient end products. The androgen derived from these precursors produce excessive virilization of a female fetus causing genital ambiguity at birth or hyperandrogenism later in life(4). The mineralocorticoids disturbance might lead to salt wasting

(21-OH or 3 B HSD deficiency) or hypertension (11-B OH deficiency). This salt wasting may be masquerade as acute gastroenteritis or septicemia in new born or infants presenting as severe dehydration(5). The genital ambiguity / virilization being a hard clinical sign, brings many of them to clinical attention. Non-classical (late onset, attenuated) 21-hydroxylase deficiency, the most common form might present as premature pubarche, peri or post pubertal hirsutism or acne or amenorrhoea rarely. Majority of cases are cryptic and are picked up by family studies only(7). 3-bHSD deficiency due to deficiency of D 4 gonal steroids presents as insufficient virilization and sexual ambiguity in male fetus but due to a large amount of DHEAS female infants are virilized. Hyperandrogenism, either of ovarian or adrenal origin manifests according to its cause, severity and age of presentation. Post pubertal hyperandrogenism may manifest as hirsutism, acne, oligomenorrhea with ovulatory dysfunction(2). Pre or peripubertal hyperandrogenism may rarely present with disturbance in secondary sexual development and achievement of menarche(8). For some strange reason hirsutism doesn't develop before the age of 12-13 years.

Evaluation of hyperandrogenism includes assessment of pattern and quantity of hair growth. If hirsutism is established (Ferriman-Gallway score >8; 5% population normally); screening is done with plasma androgens (testosterone, free testosterone & DHEAS) measurement (9). A testosterone level of <sup>3</sup> 350 ng/ml indicates a virilizing tumor (>200 ng/ml being suggestive) and if associated with > 800 ng/ml basal DHEAS, it is of adrenal origin. USG/MRI or CT abdomen usually demonstrates the mass lesion (10).

A practical abbreviated protocol of evaluation is done by dexamethasone suppression test (dexamethasone 2mg/d orally for <sup>3</sup> 4 days or 100 microgm / m<sup>2</sup>) segregating patients on the basis of response of free testosterone, DHEAS, and serum cortisol. Adequate androgen suppression (i.e. plasma free testosterone < 8 ng/ml and DHEA <70ng/ml) can be due to CAH or functional adrenal hyperandrogenism and ACTH stimulation will be abnormal. Otherwise it can be due to hyperprolactinemia or idiopathic variety but non-suppressible free testosterone. If androgens are non-suppressible, cortisol suppressibility might differentiate Cushing's syndrome from PCOS or tumoral hyper secretion(11). GnRH testing with Nafaralin 100mgm subcutaneously leading to elevation of 17-OHP (>260 mg/dl) may alternately help in diagnosis of functional ovarian hyperandrogenism or PCOS. Basal or post progesterone trial LH levels may corroborate with FOH(12). USG suggestion of polycystic ovaries may be helpful in half of PCOS patients, although stromal hyperplasia is considered to be more specific now.

Our patient presented with severe hyperandrogenism (hirsutism, masculinization and clitoromegaly) in pre pubertal stage. She had primary amenorrhoea as a

manifestation of hyperandrogenism. Investigations revealed a moderate hyperandrogenism in non-tumor range ( $T < 2\text{ng/ml}$ ) with no identifiable lesion in adrenal or ovaries. The differentiation had to be made between PCOS and CAH. Since androgens were suppressible ovarian source was unlikely. This was corroborated by low LH/FSH ratio also. Elevated basal 17 OHP suppressible with dexamethasone indicated an adrenal androgen source likely due to virilizing congenital adrenal hyperplasia. The imaging evidence of hyperplastic adrenal glands and lower basal cortisol were favorable to the diagnosis. The patient was normotensive and hence virilizing CAH due to 11-B-hydroxylase deficiency was unlikely. The NCAH due to 21-hydroxylase deficiency was the most probable diagnosis, in view of rarity of 3 $\beta$ -HSD deficiency and the absence of any family history. We conclude that while evaluating a case of primary amenorrhea we should also keep NCAH as one of the differential diagnoses particularly in our community where there is prevalent consanguinity.

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