

CASE REPORTS

Hetero sexual precocious puberty: Case report and literature review

Zujaja Hina Haroon*¹, Aamir Ijaz¹, Muhammad Asad Haroon², Shahid Ahmed³, Muhammad Amjad Pervez¹, Naveed Asif¹

¹Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan

²Department of Pediatrics, Rawalpindi Medical College, Rawalpindi, Pakistan

³Department of Clinical Endocrinology, Military Hospital, Rawalpindi, Pakistan

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is the most frequent disorder of sex development (DSD). It follows variable clinical course. We present a rare case of CAH that remained clinical enigma. A 6-year-old boy presented with increased pigmentation, deepening of voice and appearance of male secondary sexual characteristics. There was history of frequent episodes of ill health with cough, fever, diarrhea and off and on vomiting. Laboratory workup revealed Serum Sodium 138 mmol/L (Ref Values: 135-145), Serum Potassium 4.1 mmol/L (Ref Values: 3.5-5.0), Serum Chloride 101 mmol/L (Ref Values: 97-106). Hormonal profile revealed serum 17-OH Progesterone 85.9 nmol/L (Ref Values: 8.0), DHEA-S 861.9 $\mu\text{g}/\text{dl}$ (Ref Values: 125-619), Testosterone 23.2 nmol/L (Ref Values: 0.1-2.4), Cortisol 563 nmol/L (Ref Values: 138-690), ACTH 1,152 pg/ml (Ref Values: 10-85), Plasma Active Renin Mass Conc 45 $\mu\text{IU}/\text{L}$ (Ref Values: 8-35 $\mu\text{IU}/\text{L}$), Plasma Aldosterone 115 pmol/L (Ref Values: 140-2,240). X-ray bone age = 12 Y \pm 6 m depicting precocious puberty. But USG abdomen and pelvis showed small uterus (28 mm \times 13 mm \times 22 mm) and karyotype revealed 46 XX genotype. Based on typical findings, a diagnosis of CAH with heterosexual precocious puberty was established. Patient responded well to tablet Hydrocortisone 20 mg^{1/2} BD and Mineralocorticoid (Florinef) Tablets 0.1 mg OD. The aim of current report is to revisit clinical approach to DSD with special emphasis to rare presentation of CAH with heterosexual precocious puberty.

Key Words: Congenital adrenal hyperplasia, XX karyotype, Hetero sexual precocious puberty

1. INTRODUCTION

The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol,^[1] aldosterone, or both. Deficiency of 21-hydroxylase, resulting from mutations or deletions of CYP21A2, is the most common form of CAH, accounting for more than 90% of cases.^[2] Incidence is

1:5,000 to 1:15,000 live births, prevalence is as high as 1:27 in Ashkenazi Jews, Male: Female 1:1, mortality rate is 3%-13%.^[3] Clinical presentation of CAH due to 21-hydroxylase deficiency depend on severity of the enzyme deficiency. In females the spectrum can vary from very severe form (classic virilizing adrenal hyperplasia) presenting at birth with ambiguous genitalia, milder form (simple virilizing adrenal hyperplasia) can present in childhood with

*Correspondence: Zujaja Hina Haroon, Assistant Professor; Email: zhharoon@gmail.com; Address: Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan.

precocious pubic hair, clitoromegaly, accelerated growth and skeletal maturation, while mildest form (non-classic adrenal hyperplasia) can present in adolescence or adulthood with oligomenorrhea, hirsutism, and/or infertility.^[4] In males an important clinical distinction is that it does not present with ambiguous genitalia. In both sexes the severe form of enzyme deficiency may present as classic salt-wasting adrenal hyperplasia in neonatal life with failure to thrive, recurrent vomiting, dehydration, hypotension, hyponatremia, hyperkalemia, and shock.

CAH in an XX child presenting as a boy with a well-developed phallus and early appearance of facial and pubic hair is an extremely rare presentation of an otherwise rare disease. We present such a case of CAH that was born in society where birth of a male child is taken as pride and no body bothered to confirm the presence of testes and the chromosomal sex. A phenotypic male child presenting with precocious puberty; but actually a genotypic female presenting with heterosexual precocious puberty.



Figure 1. Facial features (skin pigmentation & mustaches)

2. CASE REPORT

A 6-year-old male child presented with 1-year history of increased pigmentation, deepening of voice and appearance of secondary sexual characteristics. There was history of frequent episodes of ill health with cough, fever, diarrhea and off and on vomiting. His birth, developmental and family history was unremarkable. His parents were cousins. He had one younger brother who is normal. Mother had one miscarriage before him. Physical examination revealed an average built, well oriented child with normal vital signs, weight 30 kg and height 133 cm (> 97th centile). (S) He was euvolemic clinically with normal skin turgor and there was no peripheral edema. (S) He had generalized skin pigmentation especially darkening of knuckles and palmar creases (see Figures 1, 2). Comparison can be made with his earlier photograph (see Figure 3). Genital examination revealed

hyperpigmentation of external genitalia, pubic hair (Tanner stage IV), Penile length about 6 cm fixed with scrotum (Tanner stage V), Testes not palpable, no vaginal opening (see Figure 4). Remaining examination was unremarkable.



Figure 2. Skin pigmentation especially knuckles



Figure 3. Patient at 8 months of age

Laboratory workup revealed Serum Potassium 4.1 mmol/L (Ref Values: 3.5-5.0), Serum Chloride 101 mmol/L (Ref Values: 97-106), and Serum Sodium 138 mmol/L (Ref Values: 135-145). Hormonal profile revealed serum 17-OH Progesterone 85.9 nmol/L (Ref Value: < 8.0), DHEA-S 861 µg/dl (Ref Values: 125-619), Testosterone 23.2 nmol/L (Ref Values: 0.1-2.4), ACTH 1,152 pg/ml (Ref Values: 10-85), Cortisol 563 nmol/L (Ref Values: 138-690), Plasma Active Renin Mass Conc 45 µIU/ (Ref Values: 8-35 µIU/L), Plasma Aldosterone 115 pmol/L (Ref Values: 140-2,240). The complete battery of investigation performed (complete

blood picture, fasting plasma glucose, renal function tests and liver function tests) revealed no abnormality. X-ray bone age = 12 Y ± 6 m. USG abdomen and pelvis showed bilateral adrenal glands enlarged (left adrenal 1.60 cm × 1.01 cm, right adrenal 1.57 cm × 1.13 cm), Small uterus present (28 cm × 13 cm × 22 mm), Pea size ovaries present, testes were not found in inguinal region and intra-abdomen. Karyotype revealed 46 XX genotype. Clinical diagnosis of CAH with heterosexual precocious puberty was established based upon typical findings and comprehensive workup.



Figure 4. Pubic hair & external genital development

2.1 Treatment

A thorough counseling of patient and family was undertaken, pivotal being lifelong nature of disease and importance of good compliance. Patient responded clinically and biochemically well to tablet Hydrocortisone 20 mg ^{1/2} BD and tablet Florinef 0.1 mg OD.

2.2 Outcome and follow-up

Consultant Endocrinologist advised to raise him as a girl. But due to social pressure parents insisted on raising him as a boy. They agreed to receive treatment only if male gender was maintained. They were, however, explained life-saving and lifelong requirement for treatment if continued with male gender. In future, planned to do necessary reconstructive surgery and later on give testosterone at time of natural puberty to maintain male phenotype.

3. DISCUSSION

CAH is the most common XX DSD presenting on medical floor with potentially life-threatening consequences. CAH encompasses wide phenotypic as well as genotypic variability even within members of the same family.^[5] Inheritance of 21-OHD CAH is autosomal recessive. Mostly the pathogenic variant exists as heterozygous trait in the parents. However about 1% of pathogenic variants are de novo and thus 1% cases of 21-OHD CAH are seen in children where only one parent is heterozygous for the pathogenic variant.

Assessment of a patient with suspected hyperandrogenism should include serum testosterone, 17 Hydroxyprogesterone (17-OHP) and Dehydroepiandrosterone Sulphate (DHEAS). Evaluation of androgen levels and their site of secretion are essential. Other endocrine studies as suggested by the history and physical examination, are also warranted.^[6] A basal screening level of 17-OHP of more than 2-4 ng/ml (6-12 nmol/L) mandates an ACTH stimulation test to confirm the diagnosis. A post ACTH stimulation 17-OHP level of 10-12 ng/ml (30-36 nmol/L) is consistent with the diagnosis of CAH, although some authors suggest a higher cut-off of 20 ng/ml (60 nmol/L).^[7,8] A combination of plasma testosterone concentration greater than 200 ng/dl (8.7 nmol/L) (or two to three time the upper normal range) with a normal DHEAS level is highly suggestive of an ovarian androgen secreting neoplasia. A combined increased testosterone concentration greater than 200 ng/dl (8.7 nmol/L) with an elevated DHEAS level of more than 600 µg/dl (16.3 µmol/L) is highly suggestive of an adrenal androgen secreting neoplasia.^[9] Our patient's Hormonal profile revealed serum 17-OH Progesterone 85.9 nmol/L (Ref Value: < 8.0), DHEA-S 861.9 µg/dl (Ref Values: 125-619), Testosterone 23.2 nmol/L (Ref Value: 0.1-2.4), ACTH 1,152 pg/ml (Ref Value: 10-85), cortisol 563 nmol/L (Ref Value: 138-690).

With reference to two studies of extensive clinical experience of hyperandrogenism, the different aetiologies of hyperandrogenism other than those secondary to androgen secreting neoplasias, did not have serum testosterone levels comparable to the values seen in our patient. Non classical CAH patients displayed the highest testosterone levels in the study by Carmina et al. with mean values of 3.88 ± 1.04 nmol/L (112 ± 30 ng/dl) and patients with hyperandrogenic insulin resistant acanthosis nigricans (HAIRAN) syndrome displayed the highest testosterone levels in the study by Azziz et al. showing mean values of 4.08 ± 4.74 nmol/L (111.91 ± 136.72 ng/dl).^[10,11] We followed the 2-day adrenal suppression test using 0.5 mg dexamethasone tablets as specified in the American Association of Clinical Endocrinologists (AACE) Hyperandrogenism Guidelines. The testosterone level, DHEAS and cortisol responded, pointing to adrenal source.^[6]

However, in a study by Kaltsas et al, it was concluded that the utility of this test is in distinguishing androgen secreting tumours from non-tumourous hyperandrogenism by demonstrating lack of testosterone suppression in tumour causes which is associated with 100% sensitivity and 88% specificity.^[12]

New born screening for CAH cannot be overemphasized, early detection of the disorder not only help in timely treat-

ment but also important for gender allocation of the child with genital ambiguity. Once the gender is allocated changing gender on basis of karyotyping creates a lot of psychosocial trauma both for the individual and family. In our opinion cases of CAH with 46 XX karyotype should preferably be raised as females. If treatment is started timely fertility can be well preserved. However in the study by Khattab A et al three patients of CAH with 46 XX karyotype were assigned male gender and had a successful outcome provided there is strong parental support and expert endocrine care.^[13]

Clinical criteria for diagnosis

An infant presenting with salt wasting crisis in the first four weeks of life must be suspected of CAH. These infants can have raised serum concentration of potassium, low serum concentration of sodium, chloride, and total carbon dioxide (CO₂) and inappropriately raised urine concentration of sodium. But raised level of serum 17-OHP is considered as a positive newborn screening marker for CAH. Clinically CAH is suspected in females who are virilized at birth, or who become virilized after birth, or who have precocious puberty or adrenarche. However males with masculinization in childhood (*i.e.*, premature adrenarche or precocious puberty) should also be suspected of CAH.

The laboratory diagnosis of 21-OH CAH is established with the following laboratory findings:

- (1) Elevated levels of Serum 17-OHP. If Basal sample for 17 OHP is > 45 nmol/L its Classic CAH and in such cases ACTH stimulation test for CAH is not required, however if it is < 6 nmol/L it rules out CAH. If basal 17 OHP is 6-45 nmol/L, it requires ACTH Stimulation

test (CAH). If post ACTH stimulation test 17 OHP > 60 nmol/L is suggestive of classic CAH, 45-60 nmol/L is suggestive of non-classic CAH and < 45 nmol/L is suggestive of an unaffected child.^[14]

- (2) Elevated levels of testosterone, Adrenal androgens and their precursors (androstenedione, DHEA) are seen in the affected females and pre-pubertal males.
- (3) Marked rise in the Plasma renin activity with inappropriately low serum aldosterone result in reduced ratio of aldosterone to PRA indicating impaired aldosterone synthesis. This helps in differentiating between the salt-wasting and the simple virilizing form of CAH after the newborn period.^[15]
- (4) Identification of biallelic pathogenic variants in CYP21A2.

4. CONCLUSION

Extreme virilization in CAH can cause heterosexual precocious puberty, which can be detected by proper clinical and laboratory evaluation including karyotyping. CAH can be life-threatening in neonates, so early detection by a National Newborn Screening is mandatory. With lifelong steroid replacement therapy CAH has good prognosis including maintenance of fertility, if diagnosed and managed in a timely manner.

Patient consent

Obtained.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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