CASE SERIES

FEMALE PSEUDO HERMAPHRODITISM: LATE ONSET CONGENITAL ADRENAL HYPERPLASIA

Nosheen Akhtar, Zartaj Hayat, Arifa Bari

Department of Obstetrics and Gynaecology, Foundation University Medical College /Fauji Foundation Hospital Rawalpindi-Pakistan

Non-classic congenital adrenal hyperplasia is a genetic condition caused by deficiency of 21-hydroxylase deficiency (NCAH). It is a milder and later onset form of a genetic condition known as congenital adrenal hyperplasia. We present four cases of non-classical congenital adrenal hyperplasia presented in gynae OPD foundation university medical college Fauji foundation hospital from Jan 2016 to March 2017. The presenting complaints were hirsuitim, menstrual problem and virilization of genitalia. Two girls were having primary amenorrhea while rests of two were having secondary amenorrhea. Two patients were already diagnosed as non-classical congenital adrenal hyperplasia due to ambiguous genitalia at the time of birth while the rest of two with marked clitoromegaly were diagnosed during workup in gynae OPD. Menarche was achieved successfully among those with primary amenorrhea after treatment. All four girls were referred to plastic surgery for clitoral reduction surgery. The post-surgery patient satisfaction level was high. Correct diagnosis of the disease can cure the patient instead of letting her live a life of being labeled with social stigmata of an intersex individual.

Keywords: Non-classical congenital adrenal hyperplasia; Hirsuitism; Clitoromegaly

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INTRODUCTION

Non-classic congenital adrenal hyperplasia (NCAH) is an autosomal recessive disorder. It occurs due to deficiency 21-hydroxylase which in turn occurs due to mutations in the *CYP21A2* gene, located at chromosome 6p21.[1] The clinical presentation in non-classical variant of congenital adrenal hyperplasia is androgen excess rather than that of glucocorticoids deficiency. Excess of androgens impairs hypothalamic sensitivity to progesterone which in turn result in a persistently rapid GnRH pulse frequency and increases luteinizing hormone (LH) secretion.[2] LH levels are higher in women with NCAH.[3] This LH hyper secretion initiates and maintains excessive androgen production by ovaries. Treatment of non-classical congenital adrenal hyperplasia is symptomatic. Goals of therapy are regularization of menstrual cycle, prevention of progressive hirsutism and acne and fertility. Combined oral contraceptive pills (COCs) can restore menstrual regularity and among COCs cyproterone acetate is effective for those having hirsutism. The addition of COCs and cyproterone help reduce the need for steroid therapy.[4] Steroids are also used for the treatment. Steroids reduce androgen production by adrenal. This in turn leads to restoration of ovarian function by relieving hypothalamic pituitary gonadotrpin function from the effect of excess androgens.[5] However this benefit must be balanced against the risks of steroid therapy, i.e., iatrogenic Cushing syndrome and bone loss. An elevated progesterone concentration in NCAH is considered to be aetiology for sub fertility in women with NCAH. In one study fertility rate is lower in patient with NCAH. ($p<0{\cdot}001$)[6]

CASE 1

A 16 years-old girl presented in department of Foundation University Medical College and Fauji Foundation Hospital Rawalpindi with complaint of primary amenorrhea, hirsutism and clitromegaly. Her mother has normal reproductive span with regular menstrual cycle. There was no history of galactorrhoea or weight gain. Her sister has menarche at 13 years of age with normal 3/28-day menstrual cycle. Patient was thoroughly evaluated. Her general physical examination showed marked hirsutism with Ferriman Gallway score 16 (Figure-1). Her BMI was 21 Kg/m2. Male pattern baldness and voice hoarseness was present. Pelvic examination revealed intact vaginal opening and marked clitoromegaly. (Figure-2)

She never took any over the counter medication for this problem. The laboratory investigations were performed which showed normal follicle stimulating hormone (FSH) and luteinizing hormone (LH). (FSH 3.7IU/L, LH 10 IU/L). Serum testosterone level was 11 mmol/l (0.19–2.7 nmol/L). Her karyotype was 46 XX. Pelvic ultrasound revealed normal uterus and normal bilateral ovaries. The raised testosterone level was evaluated by ultrasound abdomen, serum 17 hydroxy progesterone and dehydroepiandrosterone sulphate (DHEAS) level. Ultrasound abdomen was unremarkable. 17

hydroxy progesterone levels were raised, i.e., 82nmol/L (0.91–2.73 nmol/L) and DHEAS was 631 ug/dl (145–380 ug/dl). This confirmed the diagnosis of late onset congenital adrenal hyperplasia and patient was referred to endocrinologist. Patient had been started treatment with steroid, i.e., prednisolone 5 mg twice daily. While on steroid therapy she had onset of menstrual cycle. The hormonal profile improved and her 17 hydroxyprogesterone fell back to the level of 16 nmol/L. The steroids were tapered off gradually. She was referred to plastic surgeon for clitoral reduction surgery.

CASE 2

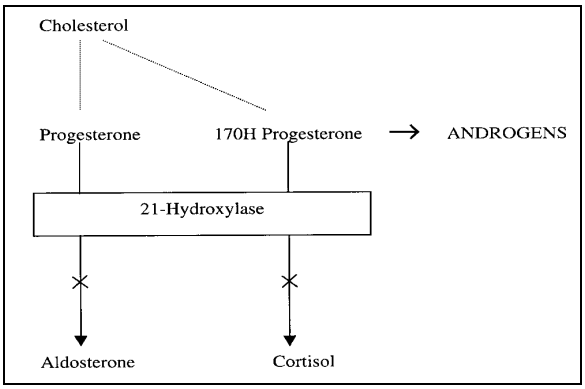
A 14 years-old girl was referred from paediatric department to the Gynae department of Foundation University Medical College and Fauji Foundation Hospital Rawalpindi. She was diagnosed case of non-classical congenital adrenal hyperplasia at the time of her birth due to ambiguous genitalia. Her detailed workup was done already with diagnosis established in paediatric department. She has history of non-classical congenital adrenal hyperplasia in her two first degree relatives both of them after treatment were cured and conceived successfully. On examination, her BMI was 20 kg/m^2. Patient was having marked hirsutism on her face and whole body with Ferriman Gallway score of 20. Her external genitalia were showing formation of micropenis along with intact vaginal orifice and hymen. Her serum testosterone level was 10 nmol/Litter (0.91–2.73 nmol/L), 17 hydroxyprogesterone was 88 nmol/ L (0.91–2.73 nmol/L) and DHEAS was 538 ug/dl (145–380ug/dl). Serum FSH was 4 IU/L FSH and serum LH was 12 IU/L. Ultrasound pelvis was unremarkable. She was started on prednisolone 5 mg twice daily by endocrinologist.

On her follow up after three months she was started with combined oral contraceptives (COCs) containing cyproterone acetate (Diane 35) but patient didn't bleed after that. Next follow up visit after three months showed no reduction in her 17 hydroxyprogesterone level the dose of steroid was increased by the endocrinologist to 5mg three times daily. Patient was counselled to wait for another 6 months and continued with steroid therapy as advised by endocrinologist but one month later she reported with onset of menstruation. Patient was referred to plastic surgeon and her reconstructive surgery was performed. The satisfaction level of patient was improved a lot in her follow up visit after surgery. The 17 hydroxyprogesterone level was 70 nmol/L the patient is still on steroid. The endocrinologist advised her to follow up after three months for review.

CASE 3 & 4

Another two young girls of ages 15 and 16 years respectively presented in gynae OPD with oligomenorrhea and androgenization of genitalia. Both were diagnosed case of non-classical congenital adrenal hyperplasia as detailed work up done at birth due to ambiguous genitalia at the time of birth. On examination both patients were having normal BMI. One of them was having marked clitoromegaly (Figure-3), hirsutism and oligomenorrhea, while the second one was having clitoromegaly but to lesser degree and oligomenorrheic cycle of 3/45.

The testosterone and 17 hydroxyprogesterone levels were raised and Ultrasound pelvis showed polycystic ovaries. The apprehension of the patients was due to male appearance of external genitalia. One of the patients was started with COCS. Both the patients were referred to plastic surgeon for clitoral reduction surgery. The patient with marked clitoromegaly underwent surgery (fig 4) and her post-operative satisfaction was high while the other patient's surgery is due.



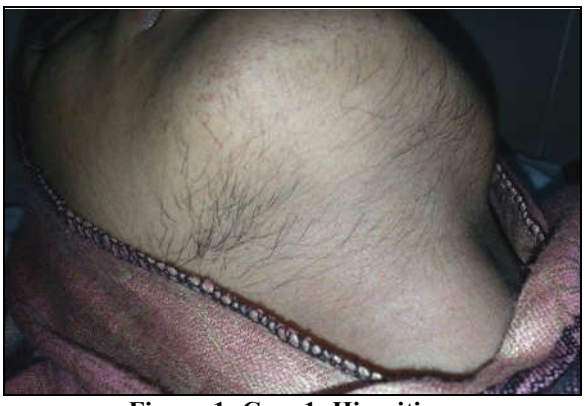


Figure-1: Case 1: Hirsuitism

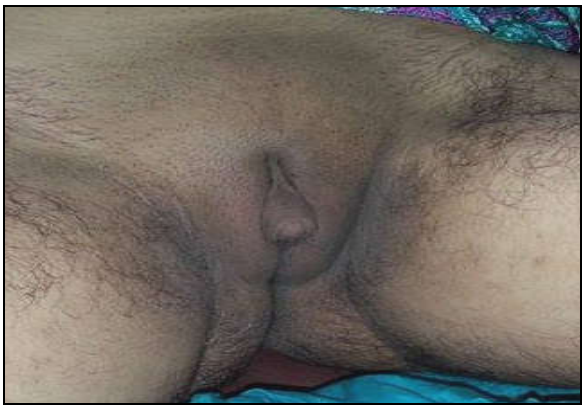


Figure-2: (Case 1) Clitoromegaly.

Figure-3: (Case 3): Marked Clitoromegaly

Figure-4: (Case 3) Post surgery

DISCUSSION

Non-classical congenital adrenal hyperplasia is an example of female pseudo hermaphroditism. The disease present with clinical features of hyperandrogenism. In a multicentre study, among adolescent and adult women with non-classical congenital adrenal hyperplasia hirsutism was the most common clinical feature (59%) followed by oligomenorrhea (54%) acne (33%). While clitoromegaly was present in 10 % of patient.[7] In another study in 161 women with NCAH the presenting clinical features were hirsutism (78%), menstrual dysfunction (54.7%), and decreased fertility (12%).[8] Women with NCAH due to chronic anovulation have oligomenorrhea, and infertility. Polycystic ovary morphology may be present in about half of women with NCAH.[9] In our four cases hirsutism was present in all four cases. Regarding menstrual irregularities two patients were having primary amenorrhea and the other two were having secondary amenorrhea. All four girls were brought by their mother being very much concerned about the appearance of external genitalia. The androgenization of external genitalia was present in all four patients with varying degree. Two of our patients have polycystic ovaries on ultrasound. The hormonal profile of all four patients showed raised level of luteinizing hormone (LH). The cut off value of testosterone requiring detailed evaluation in women presenting with features of hyperandrogenism is >5 nmol/L. All of our four patients were having testosterone levels higher than 5 nmol/litters. The LH level was also high in all four patients pointing towards the physiology of the condition. It is stated that in hyperandrogenic women measurement of a morning level of serum 17-hydroxyprogesterone (17-HP) should be included in the initial investigation.[10] Although the gold standard for diagnosis of NCAH is ACTH stimulation test however the diagnostic accuracy early morning follicular phase serum 17-OHP is quite good.[11] In one study, the use of a 17-OHP cut-off value of greater than 2 ng/mL provided a 100% sensitivity and 99% specificity for the detection of NCAH, thus making it a useful diagnostic test avoiding the need of ACTH test which is stressful and costly.[12] In our patient in whom the diagnosis was made in gynae clinic or in paediatric department the test used for diagnosis was 17 hydroxy progesterone, which was significantly raised in all four cases.

Treatment of NCAH should be directed towards symptoms. The patients diagnosed as NCAH at childhood were on low dose steroid since child hood by the paediatricians and those diagnosed at puberty were also started with steroids by the endocrinologist. Hydrocortisone is the drug of choice however prednisolone or dexamethasone can also be used. The dose of hydrocortisone is 12–18 mg/ m^2 /day while that of prednisolone is 5–7.5 mg/day. Our patients were given prednisolone. The target 17-hydroxyprogesterone range is 12–36 nmol/L.[13] However the 17 hydroxyprogesterone level of patients presenting in gynae OPD was above this range hence they were continued with steroid by the endocrinologist. The excess androgens promote premature epiphyseal closure while excess steroids

suppress growth hence a balance is required to achieve normal growth. The risk of stunted growth is more in classical adrenal hyperplasia than in NCAH and generally patient with NCAH have normal height.[14] Same was observed in our four cases and all of our four patients were having normal BMI. It is said that in adult normalization of 17 hydroxy progesterone should not be the goal of treatment and normalization of 17 hydroxyprogesterone level can be helpful in achieving fertility in women requiring so by improving receptivity of endometrium.[15] The excessive glucocorticoid scan cause bone loss, gastric ulcer and risk of adrenal suppression and patient should be given cover for all these. Two of four patients received steroids. One of them after normalization of 17 hydroxy progesterone steroids were gradually tapered off and stopped but the other patient is still on steroid by endocrinologist due to persistently high level of 17 hydroxyprogesterone. Menstrual irregularity can be treated with combined oral contraceptive pills (COCs).[16] Two of our patients were also started with COCS containing cyproterone acetate.

For hirsutism, anti-androgen containing combined oral contraceptive pills can be given.[04] In addition cosmetic measures like laser electrolysis, waxing, threading etc can be used. All patients were advised to use cosmetic measures for hirsutism. The onset of menstruation was achieved successfully in those with primary amenorrhea after treatment. In one patient, it was achieved after 6 months of steroid therapy and in the second after the increase in the dose of steroid by the endocrinologist menstruation was started. The onset of menstruation in those with primary amenorrhic girls was quiet reassuring for the patient and their mothers. The androgenization of genitalia was of great concern in our patients. The European society for paediatric endocrinology recommends that in virilised girls surgery should be done in 2–6 months of age.

However multidisciplinary team involvement and detailed informed consent are the prerequisites.[17,18] As most of the girls diagnosed with NCAH are brought up as girls their surgery in neonatal period is the standard. In our patient surgery was not done in neonatal period. The detailed counselling of mothers and patients was done after establishing the diagnosis. They were referred to plastic surgeon after detailed workup and examination. One patient has done with surgery and post surgeries follow up showed high level of satisfaction in the patient. Two patients have got appointment for surgery while one patient who has mild clitoromegaly lost to follow up probably due to mild clinical symptoms.

CONCLUSION

Non-classic congenital adrenal hyperplasia is a genetic disorder requiring multidisciplinary approach for management. The psychosocial impact of disease is quiet distressing to patient as well as for her parents. With appropriate management, the women with intersex disorder can live a normal life.

Note: 1 ng/ml=3.35 nmol/l

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Address for Correspondence:

Nosheen Akhtar, Department of Obstetrics and Gynaecology, Foundation University Medical College, Fauji Foundation Hospital Rawalpindi-Pakistan
Email: drnosheen08@gmail.com