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NON CLASSIC CONGENITAL ADRENAL HYPERPLASIA MASQUERADING AS PCOS

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Abstract : Non classic congenital adrenal hyperplasia (NC-CAH) is a common autosomal recessive disorder that can present in childhood, adolescence, and adulthood. The typical symptoms of hirsutism,oligomenorrhea, infertility, acne, and premature pubarche lead to an ascertainment bias in favor of identifying affected women. The nature of the symptoms leads to consideration of polycystic ovary syndrome in the differential diagnosis. Late-onset CAH is a recognized secondary cause of PCOS and appears to be more common than the classic variety. Although NC-CAH is a genetic disorder, the use of morning follicular phase 17-OHP concentrations and ACTH stimulation tests are essential diagnostic studies due to the complexity of the CYP21A2 locus. Once the diagnosis is confirmed, genetic analysis may be useful. The specific treatment should be individualized and directed towards the individuals symptoms and current medical needs.We present a case of 23-yearold female who presented with hirsutism, menstrual dysfunction and infertility. She was initially diagnosed as PCOS and started on treatment but without improvement and on detailed evaluationshe was diagnosed as a case of nonclassical adrenal hyperplasia and polycystic ovaries. Proper treatment of underlying etiology led to reversal of her symptoms.

Keyword : Non classic congenital adrenal hyperplasia,PCOS,17-OHprogesterone

INTRODUCTION

Nonclassic congenital adrenal hyperplasia (NC-CAH) due to P450c21 (21-hydroxylase) deficiency is a common autosomal recessive disorder due to mutations in the *CYP21A2* gene which is located at chromosome 6p21 .This disorder was first described in 1957 by Decourt et al. Reported prevalences in women with androgen excess range from 0.6% to 9%. The worldwide incidence of NC-CAH is much higher at 1:1000, with a frequency as high as 1:27 among Ashkenazi Jews. The clinical features predominantly reflect androgen excess rather than adrenal insufficiency leading to an ascertainment bias favoring diagnosis in females. Treatment goals include normal linear growth velocity and “on-time” puberty in affected children. For adolescent and adult women, treatment goals include regularization of menses, prevention of progression of hirsutism, and fertility

CASE REPORT

A 23 year old female , unmarried working as a bank employee in madurai presented to a gynaecologist with complaints of hirsutism and irregular periods for the past 3 years. She had taken cosmetic treatment for hirsutism but hair growth did not regress. Her previous menstrual cycle was 5/29 days regular with average flow. Then she developed oligohypomenorrhea with menstrual cycle of 2/65-90 days and had only spotting. Her weight has increased from 64 to 72 kg in last 2 years. However she had no history of cold intolerance, pain abdomen, vaginal discharge, urinary or bowel complaints. There was history of treatment for primary complex at 6 years of age. Family history was negative.

Lab investigations: FSH – 6 IU/L,LH – 13.9 IU/L,Serum prolactin – 18 ng/mL (normal) Her pelvic ultrasound showed polycystic appearance of ovaries and a diagnosis of PCOS was made. She was prescribed cyproterone acetate, estrogen, spirinolactone and metformin. After an initial response, there was no further improvement in her symptoms.She got married and after marriage she stopped taking cyproterone, spirinolactone & estrogen. A year later she again visited her gynaecologist for oligomenorrhea & infertility treatment. She was re-evaluated.

LH - 17.37 IU/L, FSH – 5.38 IU/L, Prolactin – 22.85 ng/mL (increased)

She was again treated as a case of PCOS with hyperprolactinemia and was started on bromocriptine and metformin in addition to cyproterone and spirinolactone. Inspite of the above treatment she did not conceive. She was referred to our institution for further evaluation.

On examination patient was afebrile,no pallor,no icterus,no cyanosis,no clubbing,no generalized lymphadenopathy,no pedal edema.Her physical examination revealed height of 158 cm, weight of 72 kg with BMI 28.9 kg/sq.m, blood pressure 130/80 mm Hg, pulse rate 76/min, Ferriman & gallway hirsutism score of 20(normal <8).Clinical examination of cardiovascular,respiratory,abdomen,CNS were normal. Her pelvic examination was unremarkable except for male type of hair growth.

Investigations: Hb-11g/dl,Total count-6800,DC-P63 L35 E02,FBS -98 mg/dl,PPBS-136 mg/dl,urea-18 mg/dl,creatinine- 0.9 mg/dl,LFT,serum electrolytes,lipid profile,thyroid function test were within normal limits.

Hormone profile:

LH- 16.2 IU/L, FSH – 5.8 IU/L (ratio of FSH to LH reversed)

Total testosterone - 216.10 ng/dL (increased)
Free testosterone – 3.56 ng/dL (0.02 – 3.09)
Early morning follicular phase 17 (OH) progesterone – 7.2 ng/mL
After ACTH stimulation
17 (OH) progesterone – 24 ng/mL

TREATMENT & OUTCOME:
A diagnosis of Non classic Congenital adrenal hyperplasia was made and she was prescribed Hydrocortisone 10 mg in the morning and evening in addition. After about 4 months she conceived.

PCOS – the revised 2003 diagnostic criteria [2,3,4]
Diagnosis of PCOS includes the presence of two out of the three listed below:
1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries
And the absence of other endocrine causes:
Congenital adrenal hyperplasia
Androgen secreting tumours
Cushings syndrome
Hyperprolactinaemia
Thyroid dysfunction
Adapted from: The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004. However, it should be noted that “polycystic ovaries” on sonography or at pathology are simply a sign of androgen excess and possibly PCOS [2.]
Polycystic-appearing ovaries alone are insufficient for the diagnosis of PCOS, and their absence is not exclusionary[2,3]. This ovarian morphology is also observed in Non classic congenital adrenal hyperplasia, androgen secreting tumours, exogeneous androgen use, Cushing’s syndrome, Hyperprolactinemia, and up to 25% of unselected women have polycystic ovaries on ultrasound, many of which are normoandrogenic with regular menstrual cycles[2]. Thus, PCOS represents unexplained functional hyperandrogenic chronic anovulation and is a diagnosis of exclusion[2,3]. Non classic Congenital adrenal hyperplasia-Partial 21-hydroxylase deficiency may present in later life, usually in the teenage years with signs and symptoms similar to PCOS .The clinical characteristics of non-classic congenital adrenal hyperplasia do not differ markedly from those in patients with polycystic ovary syndrome or idiopathic Hirsutism [2,5,6,13,17]. CONGENITAL ADRENAL HYPERPLASIA These inherited syndromes are caused by deficient adrenal corticosteroid biosynthesis. In each case, there is reduced negative feedback inhibition of cortisol, and depending on the steroidogenic pathway involved, alteration in adrenal mineralocorticoid and androgen secretion.[1] 21-hydroxylase deficiency 90% of cases of congenital adrenal hyperplasia (CAH) are due to 21-hydroxylase deficiency. The condition arises because of defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol. Reduced cortisol biosynthesis results in reduced negative feedback drive and increased ACTH secretion; as a consequence, adrenal androgens are produced in excess . [1,8] Nonclassic or “Late-Onset” 21-Hydroxylase Deficiency Patients present in childhood or early adulthood with premature pubarche or with a phenotype that may masquerade as polycystic ovary syndrome (PCOS).[1] Late-onset CAH is a recognized secondary cause of PCOS and appears to be more common than the classic variety. In some series from tertiary referral centers, late-onset 21 hydroxylase deficiency may account for up to 12% of all “PCOS” patients, but more realistic prevalence rates are probably 1% to 3%.[1] GENETICS A point mutation in exon 7 (Val281Leu) that preserves 20-50% of enzyme function accounts for about 70% of NC-CAH alleles. Because many patients are compound heterozygotes for two or more different mutant CYP21A2 alleles, a wide spectrum of phenotypes may be observed. . Other missense mutations associated with NC-CAH include P30L, P453S, and R339H. Novel mutations associated with NC-CAH include R369W and I230T . Onehalf to two-thirds of individuals with NC-CAH carry one allele encoding for a severe defect in enzyme function (which would result in classic CAH if present on both alleles) and an allele encoding a mild defect in enzyme function on the other allele. Roughly, phenotype correlates with molecular genotype and reflects the residual activity of the milder mutation. PATHOPHYSIOLOGY Steroid Biosynthesis

The precursor of all steroids is cholesterol. The cholesterol is transported to mitochondria by a sterol carrier protein. In the mitochondria, it is converted to pregnenolone in a reaction catalyzed by an enzyme known as cholesterol desmolase or side-chain cleavage enzyme. This enzyme, like most of the enzymes involved in steroid biosynthesis, is a member of the cytochrome P450 superfamily and is also known as P450scc or CYP11A1. Pregnenolone moves to the smooth endoplasmic reticulum, where some of it is dehydrogenated to form progesterone in a reaction catalyzed by 3-hydroxy-steroid dehydrogenase. This enzyme has a molecular weight of 46,000 and is not a cytochrome P450. It also catalyzes the conversion of 17-hydroxypregnenolone to 17-hydroxyprogesterone, and dehydroepiandrosterone to androstenedione in the smooth endoplasmic reticulum. The 17-hydroxypregnenolone and the 17-hydroxyprogesterone are formed from pregnenolone and progesterone, respectively by the action of 17-hydroxylase. This is another cytochrome P450, and it is also known as P450c17 or CYP17. Located in another part of the same enzyme is 17,20-lyase activity that breaks the 17,20 bond, converting 17-pregnenolone and 17-progesterone to the C19 steroids dehydroepiandrosterone and androstenedione.

Hydroxylation of progesterone to 11-deoxycortico-sterone and of 17-hydroxyprogesterone to 11-deoxycortisol also occurs in the smooth endoplasmic reticulum. These reactions are catalyzed by 21-hydroxylase, a cytochrome P450 that is also known as P450c21 or CYP21A2.

11-Deoxycorticosterone and the 11-deoxycortisol move back to the mitochondria, where they are 11-hydroxylated to form corticosterone and cortisol. These reactions occur in the zona fasciculata and zona reticularis and are catalyzed by 11-hydroxylase, a cytochrome P450 also known as P450c11 or CYP11B1.

In the zona glomerulosa, there is no 11-hydroxylase but there is a closely related enzyme called aldosterone synthase. This cytochrome P450 is 95% identical to 11-hydroxylase and is also known as P450c11AS or CYP11B2. The genes that code CYP11B1 and CYP11B2 are both located on chromosome 8. However, aldosterone synthase is normally found only in the zona glomerulosa. The zona glomerulosa also lacks 17-hydroxylase. This is why the zona glomerulosa makes aldosterone but fails to make 17-hydroxysteroids or sex hormones.

Furthermore, there is subspecialization within the inner two zones. The zona fasciculata has more 3-hydroxysteroid dehydrogenase activity than the zona reticularis, and the zona reticularis has more of the cofactors required for the expression of the 17,20-lyase activity of 17-hydroxylase. Therefore, the zona fasciculata makes more cortisol and corticosterone, and the zona reticularis makes more androgens. Most of the dehydroepiandrosterone that is formed is converted to dehydroepiandrosterone sulfate by adrenal sulfokinase, and this enzyme is localized in the zona reticularis as well. NC-CAH - partial 21-hydoxylase deficiency: With decreased 21 -hydroxylase activity, conversions of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, and progesterone(P4) to deoxycorticosterone, are impaired. Elevated 17-hydroxyprogesterone , progesterone , and androstenedione concentrations are typically found. Individuals with NC-CAH generally have adequate mineralocorticoid secretion.Another mechanism resulting in excessive adrenal androgen secretion in NC -CAH results from the alteration in enzyme kinetics due to the *CYP21A2* missense mutations. The mutated enzyme protein is synthesized, but is less efficient than the wild type. The net result is an increased precursor to product ratio, independent of ACTH levels. In addition, genetic variations at other loci may influence steroid metabolism and steroid responsiveness. Alterations in ovarian and gonadotropic function, with the appearance of a polycystic ovary-like phenotype, also contribute to the androgen excess of these patients. Functional ovarian abnormalities in patients with NC-CAH may relate to a number of etiologies, including disruption of the hypothalamic-pituitary-ovarian (HPO) axis by persistently elevated progesterones
(e.g. P4 and/or 17-OHP) or androgens. Androgen excess impairs hypothalamic sensitivity to progesterone resulting in a persistently rapid GnRH pulse frequency which favors LH hypersecretion . This LH hypersecretion initiates and maintains a vicious cycle in which excessive ovarian androgen secretion intensifies the consequences of the excessive adrenal androgen production. In fact, women with NC-CAH demonstrate higher LH concentrations than normal women. Finally, it is possible that patients with NC-CAH may experience increased androgen excess due to an alternative pathway converting either P4 or 17-OHP to more potent androgens such as dihydrotestosterone (DHT). Enzymes involved in this alternative pathway include 5-reductases and 3-hydroxysteroid dehydrogenases. The ovarian expression of 5-reductase may contribute to excessive ovarian androgen secretion in NC-CAH as well as PCOS

CLINICAL FEATURES

Females present with various clinical signs and symptoms:

Features of androgen excess: [2,15,16]

i) abnormalities of the pilosebaceous unit (hirsutism, acne, and androgenic alopecia)

ii) the hypothalamic–pituitary–ovarian axis (i.e., ovulatory and menstrual dysfunction)

iii) the hypothalamic–pituitary–adrenal axis (adrenal androgen excess).

If the androgen excess is very severe, virilization or masculinization can also be apparent. Ovulation, Menstruation and Reproductive Function :

Women with NC-CAH often present with amenorrhea (primary or secondary), chronic anovulation, and infertility. Ultrasonography may demonstrate ovarian morphology reminiscent of polycystic ovary syndrome (PCOS). Polycystic ovary morphology may be present in about half of women with NCCAH .Many women with NC -CAH are relatively fertile. However, NC-CAH carries a greater risk of subfertility, in part due to the prevailing ovulatory dysfunction. Persistently elevated levels of progesterones during the follicular phase in women with NC-CAH may interfere with the quality of cervicalmucus, impeding penetration by sperm. In addition, elevated levels of 17-OHP and/or P4 during the preovulatary (follicular) phase of the menstrual cycle may result in inadequate endometrial maturation and impaired embryo implantation.Pregnancy wastage has been reported to be increased in few studies.

Psycho social aspects:

Interestingly, an increased frequency of homosexual and bisexual orientation was also found in women with the NC form of CAH, indicating that the relatively mild prenatal androgen excess in NC CAH may be sufficient to influence psychosexual development in some cases, or that the Increased postnatal androgen levels before diagnosis can affect sexual differentiation of the brain.[11] Infertility is inextricably related to self-esteem and psychosocial adjustment.[16] Prenatal issues & Genetic counseling:[8,12,16] Infants of mothers affected with the nonclassic disorder are also at slightly increased risk of developing classic CAH. For women with NC-CAH, the risk of having a child with salt losing or simple virilizing classical forms of CAH depends in part on the probability that the father is a carrier and mother's genotype. Nevertheless, it appears that at least 50% of women clinically ascertained to have non classic CAH are compound heterozygotes for a classic and a nonclassic mutation. Accepting this figure, there is *a priori* approximately a 0.1% (1/1000) chance that a mother with non classic disease will give birth to a daughter affected with classic CAH ([50% carrier frequency of classic alleles among women with non classic disease] x [1.6% carrier frequency in general population] x [14 chance both classic alleles will be passed to the fetus] x [12 chance the fetus is female]). However data suggest that the prevalence of 21-OH-deficient CAH among live-born children of NC-CAH women is 2.5%, higher than the 0.2% calculated prevalence (Moran et al.). In addition, the risk of NC-CAH women for giving birth to at least one child affected with CAH is 3.0%. Alternatively, the prevalence of NC-CAH among children of NC-CAH mothers is approximately 15%, much higher than the predicted rate of 1:32.Also, the risk of women with NC-CAH of giving birth to at least one child affected with NC -CAH is 11.9%. A likely explanation for the higher prevalence of affected offspring noted compared with calculated is the inherent tendency for individuals to intermarry within their ethnic subpopulation. Nonetheless, these data would suggest that biochemical screening of all children born to mothers with 21-OH-deficient NC-CAH is mandatory. Early diagnosis and treatment of children with NCAH may reduce the risk of developing clinically apparent hyperandrogenism, although there are insufficient data to assess the efficacy and safety of presymptomatic treatment of NC-CAH infants and children.

Metabolic consequences:

Factors associated with increased risk for metabolic consequences cluster in women with NC-CAH.

These factors include obesity, hypertension, and insulin resistance. The androgen excess may independently contribute to this risk due to atherogenic lipid profiles.[16]

Aldosterone synthesis and sodium balance are not compromised to any clinically significant extent in patients with nonclassic 21-hydroxylase deficiency, although under stress conditions subtle abnormalities may be elicited. Likewise, cortisol synthesis during stress is not impaired to any clinically significant degree , and there have been no deaths from adrenal insufficiency reported with this condition.[8]

There are conflicting reports as to whether adult height is compromised in nonclassic CAH. Height sd scores were lower in one study compared with the population but not when compared with midparent heights. Similarly, other investigators found no differences between nonclassic patients and their unaffected siblings.[8]

DIAGNOSIS [1,2,7,8,13,14,15,16,17,18]

Randomly measured 17-hydroxyprogesterone(17-OHP) concentrations can be normal in patients with nonclassic CAH.[1,15,16]

The diagnostic evaluation of NC CAH involves:

— Determination of serum 17-OHP,

— ACTH stimulation test,

— Urinary steroid profiling,

— Genetic testing for *CYP21A2* mutations.

The diagnosis of NC CAH is most commonly based on the determination of baseline 17-OHP levels and the ACTH stimulation test. Due to the circadian rhythm of 17-OHP secretion (parallel to that of cortisol) and its adrenal (10%) and gonadal (90%) origin, it is recommended that the diagnostic evaluation in menstruating women should be performed in the follicular phase (between days 7 and 9 of the cycle) in the early morning hours. The following interpretation of results is currently proposed:

— 17-OHP levels in the follicular phase below 2.0 ng/ml (or below 1.7 ng/ml, as preferred by other authors) rules out the diagnosis of NC CAH with a high likelihood;

— 17-OHP levels between 1.7 and 2.0 ng/ml are an indication for the ACTH stimulation test;

— 17-OHP levels exceeding 4.0 ng/ml are highly suggestive of NC CAH and an indication for the ACTH stimulation test;

The ACTH stimulation test is frequently decisive in the diagnostics of NC CAH. The 17-OHP concentrations following ACTH stimulation that are typical of NC CAH are most commonly in the range of 15–100 ng/ml. Most authors consider 17-OHP levels 10 ng/ml the lowest cutoff value for the diagnosis of NC CAH although asymptomatic carriers (heterozygotes) may also fall between the values of 10 and 15 ng/ml. As in the classic forms of CAH, urinary steroid profiling (where metabolites of 17-OHP, 21-deoxycortisol, cortisol, and androstenedione are simultaneously determined) and genetic testing for *CYP21A2* mutations may prove helpful in establishing the diagnosis.

Molecular studies have identified a separate genotype of NC CAH compared to the classic forms.

Patients may carry two mild mutations on both alleles (most commonly V281L and P30L) or have combined heterozygotes with a mild mutation on one allele and a severe mutation on the other, typical of Salt wasting CAH and Simple virilizing CAH.

TREATMENT

Treatment in NC CAH is only indicated in symptomatic cases since the potential adverse effects of glucocorticoids probably outweigh any benefits.[16,17]

Glucocorticoids:

Glucocorticoid treatment in women may be considered if hyperandrogenism, menstruation disorders, or infertility is present and for children with early onset of disease and rapid progression of pubic and body hair, growth, or skeletal age.[17]

Drugs used:

While in children hydrocortisone is the basic glucocorticoid, in adults the administration of longeracting glucocorticoids given once or twice daily is more commonly recommended. The glucocorticoids used in adults include: prednisone 5.0–7.5 mg/day, prednisolone 5–10 mg/day, dexamethasone 0.25–0.50 mg/day, hydrocortisone 15–45 mg/day(divided doses).[4,7,14,16] Because of the potential detrimental effect of glucocorticoids on the fetus , various practitioners suggest that a glucocorticoid that is inactivated by placental 11-hydroxysteroid dehydrogenase type II (e.g. hydrocortisone, prednisone, and prednisolone) should be used in sexually active females who are not on a highly effective contraceptive or who become pregnant, unless specifically intending to suppress the fetal adrenal.[15,16]

Stress dosing: Although primary adrenocortical insufficiency is not observed in patients with NC CAH, patients on longterm glucocorticoid treatment may develop secondary adrenocortical insufficiency.

Hence, in distressing situations (infection, surgery,labour), they should be receiving appropriately increased doses of glucocorticoids.[7,15,16]

Goals of treatment:

Clinical:

Clinical goals of treatment include normal linear growth velocity, normal rate of skeletal maturation, "on-time" puberty, and appropriate weight status for children and adolescents.

For adolescent and adult women, goals of therapy include regularization of menstrual cycles, prevention of progressive hirsutism and acne, and fertility.[16]

Laboratory monitoring:

The therapeutic goal is to use the lowest dose of gluco corticoid that adequately suppresses adrenal androgens and maintains normal growth and weight gain.One should not attempt to achieve normal levels of 17-hydroxyprogesterone, since this requires supraphysiologic doses of glucocorticoid that may cause Cushing's syndrome. Androstenedione and testosterone levels (measurement of the latter is useful only in prepubertal children and women) should be maintained at values that are appropriate for the patient's age and sex.[16,17] However in women seeking fertility maximum suppression of 17-OHP could potentially allow maximum endometrial proliferation and improve implantation.[16] Patients should be monitored carefully for signs of iatrogenic Cushing's syndrome, such as rapid weight gain, hypertension, pigmented striae, and osteopenia.[14,17]

ADJUVANT THERAPY Hirsutism: Remission of hirsutism is the most difficult objective to achieve with glucocorticoid monotherapy, as established hair follicles are difficult to eradicate. Treatment of hirsutism may also necessitate adjunctive cosmetic methods such as laser,electrolysis, and depilatories .The use of anti-androgens (e.g. flutamide, cyproterone acetate,spirinolactone or finasteride) should also be considered in women complaining of excess unwanted hair growth or scalp hair loss (androgenic alopecia).[1,4,16]

Menstrual dysfunction & PCOS: Females with concomitant PCOS may benefit from an oral contraceptive, although this treatment would not be appropriate for patients trying to get pregnant.[14,16] In patients with insulin resistance metformin is used.[4]

Fertility and Ovulation induction: In order to induce ovulation, if glucocorticoids fail, clomifene citrate is most commonly used. Preliminarily, the preconception use of concomitant glucocorticoids appears to reduce the risk of miscarriages in NCAH patients conceiving.[4,12,16] The effect of glucocorticoids on pregnancy outcome may be mediated through an improvement in maternal hyperandrogenemia.

Elevated serum androgen concentrations have been reported to be a risk factor for early pregnancy loss and recurrent miscarriages in women with and without polycystic ovary syndrome and an association between serum androgen levels and endometrial dysfunction has been noted.[12]

Prenatal therapy: In addition, all women with NC-CAH desiring to conceive should undergo genetic screening to determine the presence of severe *CYP21A2* mutations (and, hence, the risk of having a child with CAH), and if a severe allele is present then genetic screening of the father should also be undertaken. Many of these patients benefit from preconception genetic counseling. In patients who conceive and whose child is considered at high risk for intrauterine virilization (i.e. a female infant) consideration may be given to using high dose dexamethasone suppression in early gestation.[16] Overall, the risk of a patient with NC-CAH of having a child with CAH is relatively low (2.5%).

Therefore, prenatal therapy is not warranted unless the carrier status of the mate (as well as the genotype of a nonclassic patient) is first ascertained by genotyping as part of preconception genetic counseling, unless they have had a prior child with salt-losing or simple virilizing CAH.[8,16]

CONCLUSION

PCOS represents unexplained functional hyperandrogenic chronic anovulation and is a diagnosis of exclusion. Appearance of polycystic ovaries on USG is not synonymous with PCOS. Although the frequency is relatively low, all patients with unexplained androgen excess should be screened for NC-CAH due to *CYP21* mutations, as this diagnosis has a different prognosis, a different treatment regimen, and requires genetic counseling regarding the risks of congenital transmission.[2] It should be an integral part of any approach to investigating premature pubarche, hirsutism, or the symptoms of PCO. From the foregoing discussion it is clear that the consequences of not treating NC-CAH patients appear to relate largely to infertility, menstrual irregularity, cosmetic appearance, and psychological sequelae and hence high index of suspicion is needed for identification and treatment of these patients.[9]

ABBREVIATIONS : NC-CAH - Non Classic Congenital adrenal hyperplasia; PCOS - Poly Cystic Ovarian Syndrome; 17-OHP - 17 hydroxy progesterone; P4 - Progester one.

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