Nonclassic congenital adrenal hyperplasia misdiagnosed as Turner syndrome

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Received: 17.08.2015
Review completed: 10.09.2015
Accepted: 25.09.2015

Access this article online
Quick Response Code:
Website: www.jhrsonline.org
DOI: 10.4103/0974-1208.170416

ABSTRACT

We present a patient with nonclassic congenital adrenal hyperplasia (NCAH) misdiagnosed as mosaic Turner syndrome. She presented with complaints of primary infertility. Short stature, the presence of facial hair and hoarse voice was also noted. She had primary amenorrhea and was advised for karyotype at 16 years of age, which was reported as 45, X[20]/46, XX[80], stating her as a case of mosaic Turner syndrome. Clitoroplasty was done at 21 years of age for clitoromegaly, which was noticed during puberty. The diagnosis of mosaic Turner could not explain the virilization. Therefore, we repeated the karyotype, which revealed 46, XX in more than 100 metaphases and was sufficient to exclude mosaicism. Furthermore, the endocrinological evaluation revealed high testosterone level with a normal 17 alpha-hydroxyprogesterone (17-OHP). The presence of pubertal onset virilization with a karyotype of 46, XX and raised testosterone level with normal 17-OHP level, raised the suspicion of NCAH for which adrenocorticotropic hormone stimulation test was done which confirmed the diagnosis of NCAH.

KEY WORDS: Nonclassic congenital adrenal hyperplasia, primary amenorrhea, Turner syndrome

INTRODUCTION

Nonclassic congenital adrenal hyperplasia (NCAH) due to P450c21 (21-hydroxylase) deficiency is a common autosomal recessive disorder due to mutations in the *CYP21A2* gene. This disorder was first described in 1957 by Decourt *et al*.[1] The disorder is a mild form of congenital adrenal hyperplasia (CAH), which is divided into the classical form (further divided into salt-wasting and simple virilizing) and the mild form known as NCAH. The clinical features, resulting from androgen excess, consist of, hirsutism, acne, growth acceleration, advanced bone age, clitoromegaly in females, and penile growth in males. Higher prevalence has been reported in Ashkenazi Jewish, Mediterranean, Middle-Eastern, and Indian populations. Unlike classical 21-hydroxylase-deficiency form of CAH, the disorder is not life-threatening but can cause symptoms anytime from early childhood to adulthood. While girls with classical CAH are born with abnormalities of the genitalia, patients with NCAH have normal genitals except for clitoromegaly, onset usually during puberty.

CASE REPORT

A 25-year-old female diagnosed as mosaic Turner syndrome was referred to our institution for primary infertility work up. On evaluating her history, it was found that she was on oral contraceptives for primary amenorrhea since 16 years of age. She had developed facial hair when she was 8-year-old. There was hair growth in the chest region. Her voice became hoarse and also there was a gradual enlargement of the clitoris. At 16 years, she consulted the doctor for not being able to achieve menarche. She was then advised for a karyotype evaluation, but no endocrinological investigation was carried

How to cite this article: Mishra VV, Pritti K, Aggarwal R, Choudhary S. Nonclassic congenital adrenal hyperplasia misdiagnosed as Turner syndrome. J Hum Reprod Sci 2015;8:239-41.

out. Her karyotype was reported as 45, X[20]/46, XX[80], based on which a diagnosis of mosaic Turner syndrome was given. She underwent clitoroplasty at 21 years of age and on and off laser hair removal for facial and chest hair. Her hormone profile was done for the 1st time when she was 23 years old and 17-hydroxy progesterone (17-OHP) level was 1.3 ng/ml (0.2–1.4 ng/ml), cortisol (AM) was 5–6 μg/dl (3.7–9.5 μg/dl) dehydroepiandrosterone sulfate (DHEAS) was 189.6 μg/dl (65-380 μg/dl) and serum total testosterone was 318 μg/dl (20–130 μg/dl) which was highly raised. Thereafter, she was kept on antiandrogen but the cause of raised androgen was not explored.

On examination, she was short stature. Her height is 141 cm, weight 47 kg and hirsutism was evident. Her simplified Ferriman–Gallwey score for hirsutism was 9 (≥3).[2] She had underdeveloped breast (Tanner stage II); on pelvic examination, vagina and cervix were healthy, the clitoris was looking normal (clitoroplasty done in past) and urethra was mildly displaced posteriorly. On transvaginal sonography, uterus measured 6 cm × 3 cm × 3 cm; both the ovaries were normal size with good antral follicular count [Figures 1 and 2]. Her blood pressure (BP) was normal. Her fasting glucose, follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone, and prolactin levels were within normal limits.

Virilizing features of pubertal onset with raised testosterone levels in the absence of XY cell line or SRY gene points out an adrenal pathology and at the same time contradicted the diagnosis of mosaic Turner. Hence, we repeated the karyotype and did the analysis at our own genetics laboratory; where more than 100 metaphases were counted with an automatic scanner and all the metaphases showed 46, XX [Figure 3]. A genotype of 46XX with features of virilization; normal levels of 17-OHP, Cortisol, FSH, LH, but increased levels of testosterone; normal BP; hypoplastic uterus and normal ovaries, no palpable gonads in inguinal region; all favoring NCAH. To confirm NCAH, adrenocorticotropic hormone (ACTH) stimulation test was done, which showed basal plasma 17-OHP as 2300 ng/dl and postsynacthen (60 min) as 3400 ng/dl (<900 ng/dl). The raised level of 17-OHP after stimulation was in the range of NCAH and hence the diagnosis of NCAH was reached. For genetic confirmation patient was counseled for mutation study, which the couple declined due to financial constraints. She was started on low dose steroids to suppress the adrenal production of androgens. The patient was recruited for antagonist protocol of *in vitro* fertilization (IVF) through which 4 mature ova was retrieved. Earlier, she had been counseled for donor oocyte program considering her a case of mosaic Turner.

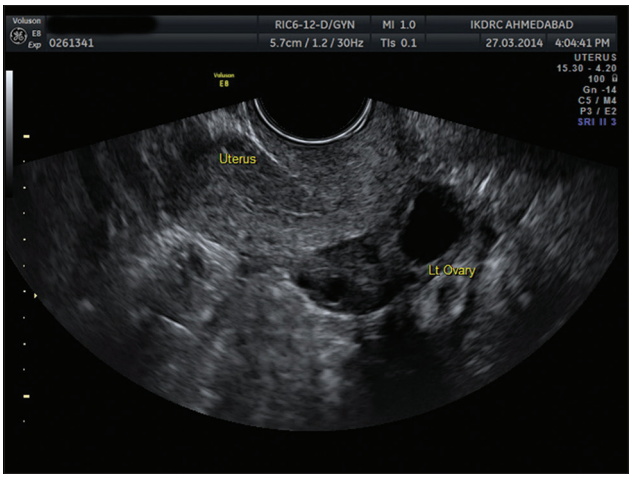

Figure 1: Transvaginal sonography showing hypoplastic uterus and normal left ovary

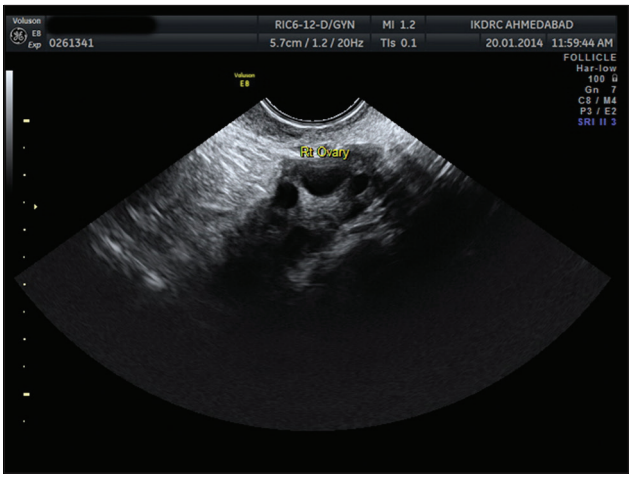

Figure 2: Transvaginal sonography showing normal right ovary with antral follicles

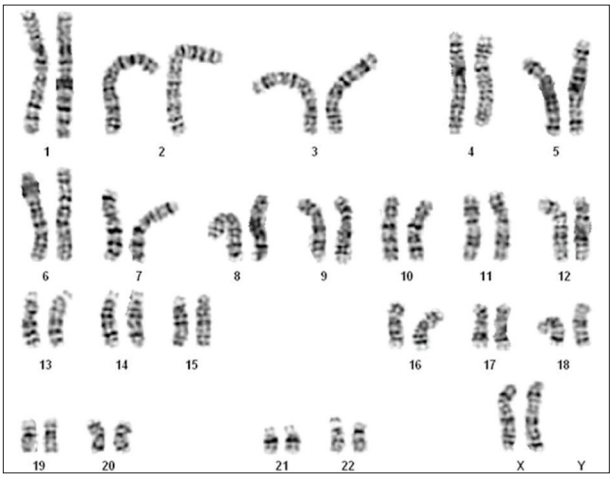

Figure 3: Karyotype showing normal female genotype with two X chromosome

DISCUSSION

Inherited adrenal enzymatic deficiencies causing hyperandrogenic symptoms sometime after birth are defined as NCAH, in contrast to the classic or congenital form of the disease in which the clinical features are apparent at birth.[3,4] NCAH can manifest itself in a number of ways in the adolescent and adult population. Women may develop irregular menstrual periods, acne, hirsutism, loss of hair on the scalp, and infertility. Some women may develop the polycystic ovarian syndrome. As adults, they may be shorter than other members of the family. The number of symptoms and their severity are different in everyone; some may remain asymptomatic and are diagnosed incidentally on genetic testing.

The presence of virilizing features at puberty advocates for an endocrinological evaluation along with karyotype to identify the cause for virilization for timely intervention and prevention of manifestations. Although, the patient had classical findings such as clitoromegaly at puberty with signs of virilization, along with primary amenorrhea, the case was misdiagnosed as mosaic Turner where virilization is not noted. In this patient, early morning levels of 17-OHP and adrenal androgens were elevated, and 17-OHP levels further increased to levels seen in NCAH after administration of ACTH.[5] As basal levels of 17-OHP can be normal in NCAH,[6] an ACTH stimulation test remains an important tool in the evaluation of children with signs of sex or age inappropriate virilization.

In an ideal situation, mutation study in the couple should be done before commencing IVF treatment because if the husband is heterozygous for the mutation of *CYP21A2* gene then the chance to have an affected child is 25%. However, it is rare that husband might be carrying the same mutation and even if he turns out to be a carrier, one can diagnose this condition after birth and start steroid before puberty to prevent virilization. Furthermore, these women carry approximately 2.5% risk of giving birth to a child with CAH, whereas the risk of having a child with NCAH is at least 15%.[7] Therefore, preconception screening and diagnosis of 21-OH-deficient NCAH is important before planning for pregnancy. Prenatal diagnosis is also possible by molecular genetic techniques.[8]

The goals of therapy for adolescent and adult women include regularization of menstrual cycles, prevention of progressive hirsutism and acne, and restoring fertility which can be accomplished by oral contraceptives, antiandrogens (e.g., flutamide, cyproterone acetate, or finasteride) and glucocorticoids.[1,9]

CONCLUSION

NCAH is a widely under-diagnosed disease causing a variety of hyperandrogenic symptoms, which are easily treated with glucocorticoid therapy. In a female child, presenting with virilizing features at puberty, the possibility of NCAH should be borne in mind. Initial tests to be advised are karyotype, adrenal steroid precursors (17-OHP, androstenedione, and DHEAS) and serum total testosterone. Although NCAH is a genetic disorder, the use of morning follicular phase 17-OHP concentrations and acute ACTH stimulation tests are essential diagnostic studies due to the complexity of the CYP21A2 locus. Genetic analysis may be considered, once the diagnosis is confirmed. The timely diagnosis and intervention in the form of steroids before puberty can prevent the unwanted virilization and fertility could be restored naturally.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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