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Case Report

DE LA CHAPELLE SYNDROME (XX MALE)

Anupama Bahadur., Anoosha K Ravi*., Shivaani Arora., Modalavalasa Swetha Sri and Rajlaxmi Mundhra

Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Rishikesh

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ABSTRACT

de la Chapelle or 46 XX sex reversal disorder is a rare autosomal recessive condition. Though genotypically a female pattern, the phenotype can be male depending on whether or not there is SRY gene. The biochemistry of such a case is that of hypogonadism with low testosterone and high gonadotropins. The gold standard for diagnosis is chromosomal analysis with fluorescent in situ hybridization (FISH) for SRY gene. Management should be individualized to the case. Here we describe one such case of de la Chapelle syndrome.

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INTRODUCTION

The XX male or de la Chapelle Syndrome is a rare sex chromosomal disorder inherited in an autosomal recessive manner. The gonadal development is affected causing male sterility. de La Chapelle first described it in 1964 and this unique syndrome has an incidence of 1 in 20,000-25,000 newborn males (de la Chapelle A *et al*., 1964, de la Chapelle A, 1981).This is a poorly characterized form of male peripheral hypogonadism with the concerned male having 46 XX chromosome instead of the normal 46 XY. The signs and symptoms of these infertile males include small stature, gynecomastia, feminine pubic hair distribution, hypospadias, undescended testis, small testis, reduced libido and reduced hormone production leading to low testosterone levels and high FSH and LH levels.

Phenotypically there are three groups of 46 XX sex-reversal individuals. In the first classical group normal male phenotype is present. The second group comprises of males with ambiguous genitalia and the third group consists of true hermaphrodites (Boucekkine C *et al*., 1994). In 2006 a revised nomenclature (the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology, 2006) was proposed according which XX male or XX sex reversal has been renamed as 46XX testicular disorder of sex development (Hughes IA *et al*., 2006).

CASE REPORT

A 37-year-old male, marital life of 4 years presented with inability to father a child. He also complained of loss of libido with no ejaculation. He was born out of a non-consanguineous marriage with male external genitalia and had normal developmental milestones according to age.

On examination he was short statured with a height of 155cm, weight of 75kg and a body mass index (BMI) of 31.21 kg/m2. His stretch penile length (SPL) was 5 cm, testes were firm in consistency and bilateral testicular volume (TV) was 2 ml.His facial, axillary and pubic hair was sparse in density and distribution and there was bilateral gynecomastia present.

His investigations revealed normal liver and renal function tests. Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) levels were elevated with low serum testosterone and normal estradiol. He was a known case of hypothyroidism on treatment. Semen analysis could not be done due to aspermia. A testicular biopsy was done which revealed seminiferous tubules without any spermatogenic activity. On Chromosomal analysis of the peripheral blood using 72 hours stimulated culture with GTG banding, a female pattern i.e.,46 XX was revealed (Figure 1). Fluorescent in situ hybridization (FISH) for determining the presence of sex determining region of Y chromosome (SRY) by multicolor DNA probe could not be done due to financial constraints.

A thorough counselling of the patient and the couple was done. The patient was started on androgen replacement therapy under the care of endocrinologist. Couple's major concern being the fertility, intrauterine insemination (IUI) with donor sperm was offered. The couple had a successful IUI cycle at the first attempt and has been blessed with a healthy female child.

Corresponding author:* **Anoosha K Ravi
Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Rishikesh

DISCUSSION

A male with a female karyotype is quite intriguing and arouses interest because of the clinical, endocrinological and epigenetic features of phenotype-genotype mismatch. Ninety percent of these patients have Y chromosomal material including the SRY gene (Ergun-Longmire B *et al*., 2005). In the rest 10% of cases due to the absence of SRY gene there are severe abnormalities of sexual development (Vorona E *et al*,. 2007). Y sequences are usually located on the distal tip of the short arm of the X chromosome. These XX males have masculine development despite normal female chromosome constitution. In case of lack of Y chromosome gene, which regulates the differentiation of Sertoli cells, there will be testicular atrophy.The role of key genes leading to abnormal sexual differentiation is known but the heterogenous and complex nature of this rare syndrome leaves many questions unanswered.

The approach to a patient with hypogonadism warrants a karyotype and if the result is 46XX then polymerase chain reaction (PCR) study should be done for the translocation of the SRY region on the Y chromosome to the distal end of the short arm of X chromosome. This confirms the diagnosis of this rare syndrome. Testicular biopsy is not required in these patients as cytogenetic analysis is sufficient.

As a clinician one has to differentiate between de la Chapelle syndrome and Klinefelter syndrome with absence of dysmorphism in the former. Family history can be present in patients with de la Chapelle syndrome.

After establishing the diagnosis of de la Chapelle syndrome, androgen replacement therapy is initiated as early as possible. Genetic counseling and psychological support should be offered to patients who need it. The prognosis of these patients is good except for infertility that is managed on individual basis.

CONCLUSION

de la Chapelle syndrome or 46 XX male is a rare chromosomal disorder. The affected male can have varied phenotype ranging from normal, ambiguous genitalia to true hermaphrodites. Like the present case, they may present later in life with complaints of infertility. Diagnosis is by chromosomal analysis and management is by androgen replacement therapy. The couple inevitably need artificial reproductive techniques for fertility.

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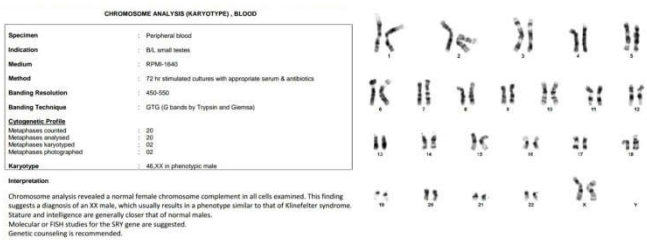

CHROMOSOME ANALYSIS (KARYOTYPE) , BLOOD

Specimen	: Peripheral blood
Indication	: B/L small testes
Medium	: RPMI-1640
Method	: 72 hr stimulated cultures with appropriate serum & antibiotics
Banding Resolution	: 450-550
Banding Technique	: GTG (G bands by Trypsin and Giemsa)
Cytogenetic Profile	
Metaphases counted	: 20
Metaphases analysed	: 20
Metaphases karyotyped	: 02
Metaphases photographed	: 02
Karyotype	: 46,XX in phenotypic male

Interpretation

Chromosome analysis revealed a normal female chromosome complement in all cells examined. This finding suggests a diagnosis of an XX male, which usually results in a phenotype similar to that of Klinefelter syndrome. Stature and intelligence are generally closer that of normal males.
Molecular or FISH studies for the SRY gene are suggested.
Genetic counseling is recommended.

Figure 1 Chromosome analysis with GTG banding revealed 46XX karyotype

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