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Case report

Exploring uncharted territory: A case report on de la Chapelle syndrome presenting as male subfertility

Sivalingarajah Raguraman [a], Balasingam Balagobi [b], K.A.U.C. Dayananda [c,*], H.M.P.B. Thilakarathne [c], Mahalingam Aravinthan [d]

[a] Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Jaffna, Sri Lanka
[b] Department of Surgery, Faculty of Medicine, University of Jaffna, Sri Lanka
[c] University Unit, Teaching Hospital, Jaffna, Sri Lanka
[d] Teaching Hospital, Jaffna, Sri Lanka

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ABSTRACT

Introduction: De la Chapelle Syndrome, also known as 46 XX disorders, is a genetic condition that affects sexual development and presents challenges, in physical, hormonal, and genetic aspects.
Case presentation: This case study explores a 42-year man with de la Chapelle Syndrome who experienced primary subfertility for eight years. The patient demonstrated delayed development of secondary sexual characteristics, shrinking testes and sparse hair distribution. A team comprising fertility specialists, uro surgeons, endocrinologists and genetic counselors collaborated to develop an approach. Based on the patients 46 XX karyotype without sex-determining region Y gene mutation assisted reproduction using donor sperm was chosen as the option. The report delves into the genetics of both sex-determining region Y gene positive and sex-determining region Y gene negative cases while emphasizing the significance of conducting thorough evaluations for issues related to sexual differentiation.
Discussion: Management strategies encompass an approach tailored to factors such as age, fertility desires and level of virilization exhibited by the patient. Surgical interventions, hormone treatments and psychological support all play roles in the management. Limited fertility treatment options are available for cases involving XX syndrome with testes such as intrauterine insemination using donor sperm and assisted reproduction with donor sperm. This case underscores the difficulties associated with delayed diagnosis.
Conclusion: Highlights the importance of adopting an approach that addresses fertility concerns along with endocrine issues and psychological support when managing de la Chapelle Syndrome

1. Introduction

Disorder of sex development (DSD) is included as a condition presenting with abnormal development of reproductive organs and genitals with an overall incidence of 1 in 4500 births[1]. It constitutes a multifaceted and diverse array of conditions that can substantially impact an individual's physical, psychological, and social well-being. The de la Chapelle syndrome, also known as 46 XX testicular disorders, is one of the rare genetic disorders that influence sexual development. It is a distinctive genetic condition characterized by the incongruity between chromosomal and phenotypic sex with an incidence of 1:20,000 to 25,000 among male infants [1,2]. This condition is further classified into sex-determining region Y gene (SRY) -positive and SRY-negative individuals, depending on the presence or absence of SRY gene on the X chromosome due to translocation. The SRY gene typically resides near the end of the Y chromosome, but it can be located on the X chromosome through translocation. The affected individuals are raised as male gender identity in childhood. However, they have diverse forms of disorders affecting their physical, hormonal, and genetic aspects of sex development, especially undescended testes and potential infertility due to azoospermia due to this structural chromosomal anomaly in their later life. [1–4]. We hereby report a rare case of de la Chapelle syndrome. A 42-year-old male presented with primary subfertility for eight years. This case report adheres to the SCARE Criteria to maintain ethical

* Corresponding author at: Hospital Road, Jaffna, Sri Lanka.
E-mail addresses: raguraman@univ.jfn.ac.lk (S. Raguraman), drudarachinthaka123@gmail.com (K.A.U.C. Dayananda), m29374@pgim.cmb.ac.lk (H.M.P.B. Thilakarathne).

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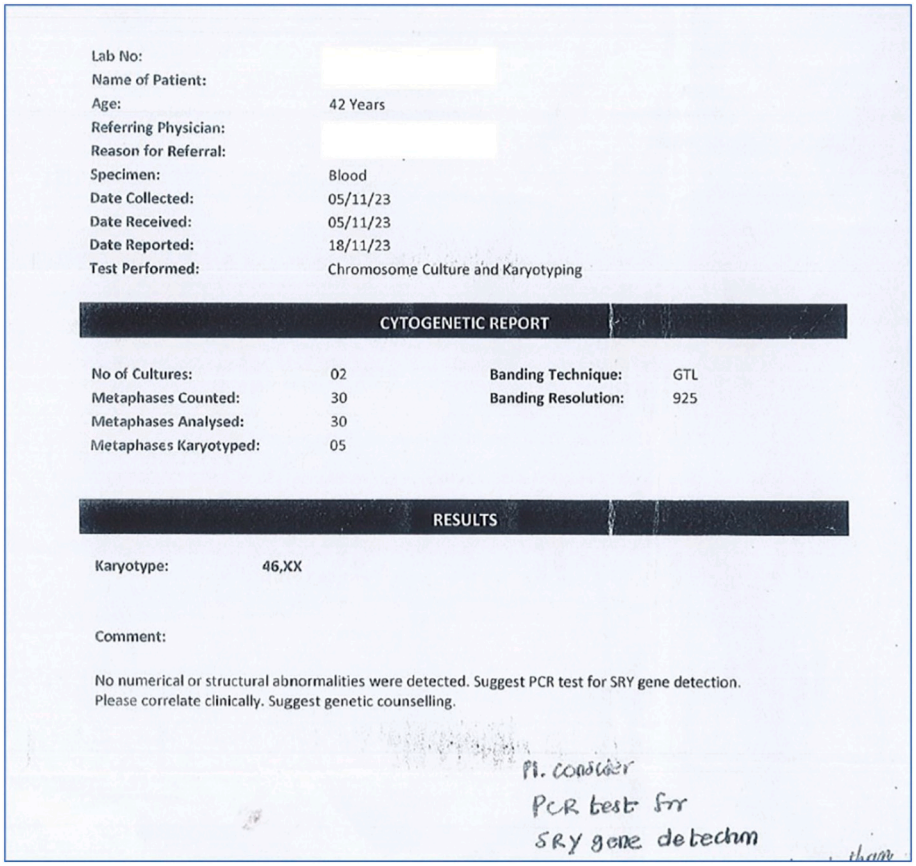
standards and integrity in scientific reporting [13].

2. Case presentation

A 42-year-old gentleman seeks fertility treatment with her 38-year-old female partner following eight years of primary subfertility. He had global developmental delay up to the age of 3 and delayed secondary sexual characteristics such as lack of focal hair distribution. He underwent surgery for gynecomastia at the age of 16. He has type −2 diabetes on metformin without good glycemic control for three years. He maintained a normal libido with occasional early morning erections during the initial two years of marriage in which they had regular sexual intercourse. However, his erection and libido have gradually reduced subsequently, which prompts the consultation. He presented phenotypically as male with a BMI of 23.8 kg/m^2. Physical examination revealed a lack of focal hair distribution, especially on the face, but his axillary and pubic hair development corresponds to Tanner stage 4. His pulse rate is 88 bpm, and his blood pressure is 130/90 mmHg, with no remarkable cardiovascular, respiratory, or neurological findings. He has a normal abdominal examination and is devoid of palpable masses, including in inguinal regions. His bilateral testes are atrophic, each measuring less than 1CC, and the penis appears small, with no evidence of varicocele, hydrocele, or inguinal hernia. Laboratory investigations revealed normal blood count and renal, liver, and thyroid functions. His FSH is 43.74 mIU/mL, and his Random blood sugar is 311 mg/dl. Abdominal ultrasound indicates a normal with a small prostate gland. Scrotal ultrasound reveals bilateral small-volume testes, with the right measuring 0.5 cc and the left 0.6 cc without varicocele, hydrocele and inguinal hernia. Karyotype analysis yields 46 XX without numerical or structural abnormalities detected (Figs. 1, 2). SRY gene mutation was not detected in the PCR test. Multidisciplinary teams, including fertility specialists, uro-surgeons with special interests in male subfertility, endocrinologists and Genetic counselors, have made a collective decision of assisted reproduction with donor sperm. Concurrently, glycemic control is managed by an endocrinologist, and psychological counselling is provided by a professional counsellor.

3. Discussion

The *SRY* gene provides instructions for making a protein called the sex-determining region Y protein or testicular determining factor (TDF), which plays a pivotal role in male sex development. The presence of the SRY gene is instrumental in shaping the masculine phenotype. The SRY gene, typically located near the terminal part of the Y chromosome, can translocate to the X chromosome during meiosis. Notably, even without a Y chromosome, offspring from a sperm cell carrying an X chromosome with the SRY gene can develop as phenotypic males. This condition is referred to as SRY-positive 46, XX testicular DSD [1–4]. In 46 XX male syndromes, 90 % of patients harbour Y chromosomal material, including the SRY gene. Ambiguous genitalia tend to be more prevalent in 46 XX male syndrome cases lacking Y chromosome material and the SRY gene. While this theory is widely discussed, alternative possibilities include an X-linked somatic mutation or Y mosaicism exclusive to the gonads, which are also possible mechanisms. SRY-positive XX males possess two X chromosomes, one of which carries genetic material from the Y chromosome, specifically the SRY gene. Conversely, XX males without the SRY gene (SRY negative) may develop a male phenotype through an alternative gene on one of the autosomes, instigated by an erroneous exchange of genetic material between chromosomes during the development of the affected individual's father's sperm cells. Despite the chromosomal configuration being more characteristic of females, the presence of the SRY gene imparts a male phenotype [5–7]. In this case, a patient with 46 XX without SRY gene mutation and the molecular level analysis of possible mechanisms of this condition was not explored since



Lab No:
Name of Patient:
Age: 42 Years
Referring Physician:
Reason for Referral:
Specimen: Blood
Date Collected: 05/11/23
Date Received: 05/11/23
Date Reported: 18/11/23
Test Performed: Chromosome Culture and Karyotyping

CYTOGENETIC REPORT

No of Cultures:	02	Banding Technique:	GTL
Metaphases Counted:	30	Banding Resolution:	925
Metaphases Analysed:	30		
Metaphases Karyotyped:	05		

RESULTS

Karyotype: 46,XX

Comment:

No numerical or structural abnormalities were detected. Suggest PCR test for SRY gene detection.
Please correlate clinically. Suggest genetic counselling.

Pl. consider
PCR test for
SRY gene detection

Fig. 1. Cytogenic report.

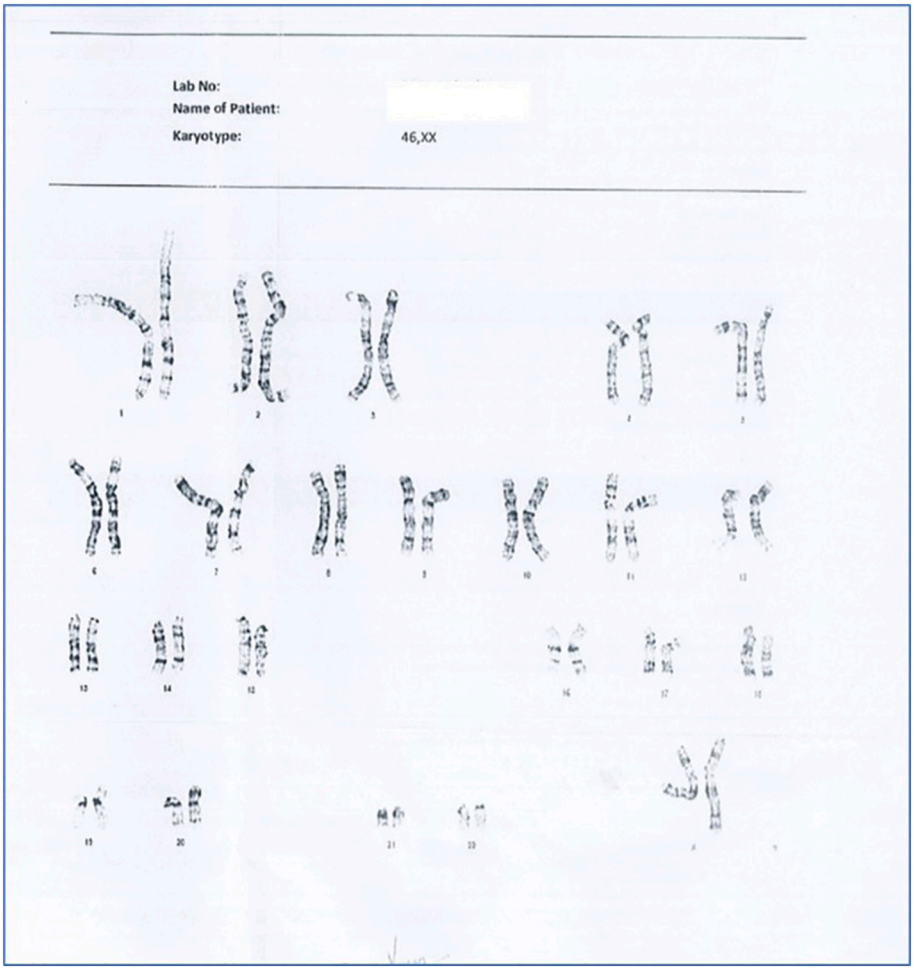


Fig. 2. Karyotype analysis.

it will not influence the management of this couple, especially in a poor resource setting.

The comprehensive evaluation of patients suspected of sexual differentiation issues, including hormonal assessments, karyotyping, and imaging studies, is crucial to uncover underlying genetic and anatomical abnormalities. The absence of radiological evidence of testes is investigated using anti-Müllerian hormone (AMH) as a marker of testicular tissue in cases of ambiguous genitalia, considering various potential causes for low AMH levels [1,5,12] . Managing the de la Chapelle syndrome typically involves a multidisciplinary approach, incorporating fertility specialists, endocrinologists, geneticists, and urologists. The patient's age guides treatment options, fertility wishes and degree of virilization, and it focuses on the precise diagnosis, early stabilization, gender of-rearing decisions, surgical intervention, hormonal treatment, psychological counselling and support. Surgical intervention is often recommended for ambiguous genitalia, addressing any remaining Müllerian duct remnants and correcting hypospadias. The surgical approach may vary based on the size of the Müllerian duct remnant and the patient's fertility desires, including procedures such as vaginectomy, uterine removal, and gonadectomy [8,9]. In patients without fertility wishes, testosterone replacement therapy for androgen deficiency and surgical correction for external genital anomalies to prevent social and sexual challenges with adequate counselling about the conditions are primary treatment options. On the other hand, limited fertility treatment options are available in couples with male DSD, especially Male XX syndrome, due to nonfunctional testis [10]. Donor sperm intrauterine insemination, Donor sperm assisted reproduction, and adoption are the possible fertility treatment options in this couple [10,11]. In this case, also, a Multidisciplinary team was involved in the diagnosis and planning of the management, and since this couple is keen on fertility management, it was focused on fertility along with Diabetic control and psychological optimization.

This case illustrates a patient with a disorder of sex development, identified as the de la Chapelle syndrome, characterized by a 46XX karyotype with a male phenotype. Late presentation of the couple with fertility wishes leading to late diagnosis of this condition during the subfertility workup would challenge clinicians to counsel and manage couples. In this case, fertility treatment, sexual life and psychological support are the main challenges, along with endocrine problems such as uncontrolled diabetic mellites. Since the couple presented late with the fertility wishes, management needs to focus on fertility treatment. Assisted reproduction with the donor sperm is a possible fertility treatment option for this couple. This couple is socially and psychologically deprived due to subfertility and our main expectation was conceived them with most convenience method.

In the meantime, psychological support and relevant hormone replacement are also essential for the holistic approach.

4. Conclusion

This case report highlights the complexity of de la Chapelle syndrome, a rare genetic disorder characterized by 46 XX testicular DSD. Its diverse clinical presentations, often due to negative SRY gene mutation and late diagnosis with fertility desires, underscore the importance of a multidisciplinary team for diagnosis and individualized management. While primary subfertility was evident, management extends beyond

fertility treatment to address endocrine and psychological issues crucial in DSD. Late presentation of DSD can burden individuals and families, challenging clinicians to address all aspects of care. Early identification and comprehensive reproductive health education are imperative for optimal outcomes alongside treatment options for DSD.

Ethical approval

Hence, our Institutional Review Board does not require ethical approval for reporting individual cases, the ethical clearance is not necessary for this study.

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Author contribution

Study concept – SR, BB, MA
Data collection – CD, BT
Interpretation - SR, BB, CD, BT, MA
Manuscript preparing – SR, BB, CD, BT

Guarantor

Dr. S. Raguraman
Consultant Obstetrician and Gynaecologist
Department of Obstetrics and Gynaecology
University of Jaffna
Sri Lanka.

Research registration number

N/A

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors have no competing interests.

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