Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/20509
DOI URL: http://dx.doi.org/10.21474/IJAR01/20509

RESEARCH ARTICLE

GENETIC INFERTILITY: EXPLORING SIX RARE CASES

Fatima-Zahra Mounassib, Ibtissam Bellajdel, Hafsa Taheri, Hanane Saadi and Ahmed Mimouni

Manuscript Info

Manuscript History
Received: 26 December 2024
Final Accepted: 28 January 2025
Published: February 2025

Key words:-
Genetic Infertility, Klinefelter Syndrome, Jacob's Syndrome, Kallmann-De Morsier Syndrome, Azoospermia

Abstract

Infertility is a multifaceted and diverse condition influenced by various biological factors, affecting either men, women, or both partners. According to a 2010 estimate by the World Health Organization (WHO), approximately 48.5 million couples worldwide were affected by infertility, with its prevalence increasing due to the growing global population (8). Genetic factors are implicated in around 30% of infertility cases (9). This article presents a case of Jacob's syndrome, four cases of Klinefelter's syndrome, and one case of de Morsier Kallmann syndrome.

Introduction:-

Infertility affects around 10-15% of couples, with male factors playing a role in approximately half of these cases. It was once believed that infertility was not hereditary, but growing evidence now suggests that many instances are due to genetic abnormalities, some of which are inherited.

Cases Report:

-Klinefelter syndrome:

Case 1: 47-year-old, with no significant pathological history, primary infertility for 10 years, clinical examination revealed reduced facial hair, large size and gynoid morphotype, testicles of normal size on testicular ultrasound, azoozpermia on spermogram, and karyotype : chromosomal formula of 47,XXY in favour of Klinefelter's syndrome with the presence of two X chromosomes and one Y chromosome of normal size and structure on all mitoses observed.

Case 2: 40-year-old with no pathological history, primary infertility for 8 years, clinical examination unremarkable, testicular ultrasound revealed small right and left testes, spermogram showed azoozpermia, karyotype showed chromosome formula 47,XXY in favour of Klinefelter's syndrome, with two X chromosomes and one Y chromosome of normal size and structure in all observed mitoses.

Case 3: 37 years old, no significant pathological history, primary infertility for 10 years, clinical examination unremarkable, spermogram showed azoozpermia, karyotype: chromosome formula 47, XXY in favour of Klinefelter's syndrome with the presence of two X chromosomes and one Y chromosome of normal size and structure on all mitoses observed.

Case 4: 38-year-old, chronic smoker for 10 years, primary infertility for 11 years, clinical examination revealed gynecomastia and large stature, testicular ultrasound revealed a single small right testis, spermogram revealed

Corresponding Author:- Fatima-Zahra Mounassib

azoozpermia, and karyotype: chromosomal formula of 47,XXY in favour of Klinefelter's syndrome, with the presence of two X chromosomes and one Y chromosome of normal size and structure on all the mitoses observed.

-Jacob's syndrome:
Patient aged 36, no pathological ATCDS of note, primary infertility for 7 years, on clinical examination large stature, macrocephaly, low-implanted ears, on spermogram severe oligospermia and severe asthenospermia, and on karyotype: chromosomal formula of 47,XYY in favor of Jacob's syndrome with the presence of an X chromosome and two Y chromosomes of normal size and structure on all mitoses observed.

-Kallmann de Morsier syndrome:
27 years old, with no notable pathological history. Married for 7 years, she had wanted to become pregnant for 6 years. At the age of 23, the diagnosis of Kallman-De Morsier syndrome was made on the basis of hyposmia associated with primary amenorrhea. A pituitary MRI was ordered, revealing the absence of olfactory bulbs and the presence of a tract, as well as a hormone assay with estradiol levels dropping to less than 10pg/ml, LH: 2.36mUI/ml FSH: 6.08

She was then put on hormone replacement therapy, with normalization of estradiol levels (61pg/ml). Induction treatment with a synthetic version of human follicle-stimulating hormone (FSH) was then initiated, resulting in a pregnancy that was carried to term, and the patient gave birth to a live baby girl by cesarean section for surgical pelvis.

Discussion:-

The World Health Organization (WHO) defines infertility as the inability of a couple to conceive after two years of regular, unprotected sexual intercourse (1).

Klinefelter Syndrome:
Klinefelter's syndrome was first describedin 1942 by Klinefelter, Reifenstein, and Albright, who identified the combination of small, firm testes, hyalinized seminiferous tubules, gynecomastia, elevated gonadotropin levels, and azoospermia. It is one of the most common chromosomal disorders, occurring in approximately 1 in 660 male births (2). Klinefelter syndrome is the leading genetic cause of hypogonadism and infertility in men, with around 11% of men with azoospermia affected by the condition (3).

In 1949, Barr and Bertram made a significant discovery when they identified dense chromatin masses, now known as Barr bodies, in the nerve cell nuclei of female but not male cats. This finding led to the use of Barr body identification in somatic cell nuclei of females to help determine genetic sex, which could be compared with phenotypic sex (5). In 1956, two groups of researchers used buccal smears to identify Barr bodies in seven patients with Klinefelter syndrome (6). In 1959, Jacobs further advanced this by discovering that a Klinefelter patient had 47 chromosomes, including an extra X chromosome (47,XXY karyotype), confirming that the Barr body in these cases represented an additional X chromosome (7).

The treatment for Klinefelter syndrome primarily involves testosterone replacement therapy to address androgen deficiency and promote appropriate virilization. This therapy has been shown to improve mood, enhance self-esteem, and protect against osteoporosis, although it does not reverse infertility (4).

-Jacob's syndrome:
Jacob's syndrome, or double-Y syndrome, is the presence of an excess Y chromosome. Its prevalence is estimated at 1/1000 births. It is related to Klinefelter syndrome. It is often responsible for mental retardation and behavioral disorders. The XYY phenotype includes a statural advance, as well as a dysmorphic syndrome with macrocephaly, clinodactyly, hypotonia and hypertelorism. Increased testicular volume is often observed(10). Fertility may be normal, but histological lesions of the gonad have been described, which may lead to impaired spermatogenesis(11). Our patient's spermogram showed severe oligospermia and asthenospermia.

-Kallmann de Morsier syndrome:
Kallmann de Morsier syndrome associates anosmia (olfaction deficit) with hypogonadism.

Hypogonadism is due to a deficiency in GnRH, a hypothalamic hormone that controls pubertal gonadal development via the pituitary gland. It is 4 times less common in girls than in boys. In fact, its incidence is around 1 in 10,000 boys and 1 in 50,000 girls(12). Most cases are sporadic. In familial forms, three modes of transmission have been described: X-linked recessive, autosomal dominant and, more rarely, autosomal recessive.

In 1954, anatomopathologist de Morsier presented a review of published cases of complete or partial absence of the bulbs and olfactory tracts in individuals suffering from hypogonadism.

Kallmann's syndrome is secondary to a defect in the development of the olfactory system and embryonic migration of GnRH-synthesizing neurons. It is rare in women (2).

This syndrome is generally diagnosed in adolescence, in the absence of spontaneous puberty, as in our patient's case. Diagnosis is based on the association of hypogonadism and hyposmia (or anosmia), detected on questioning or by olfactometric tests that quantify the response to different odorant molecules. (4)

In the event of clinical suspicion of Kallmann syndrome, a blood test is required, revealing hypogonadotropic hypogonadism (low serum estradiol concentrations in girls, sometimes below the detection threshold), with low or paradoxically normal plasma LH and FSH levels. In our case, the biological work-up showed a collapsed estradiol level with normal FSH and LH levels at the lower limit(4).

MRI is essential to confirm the diagnosis of Kallmann de Morsier syndrome, by analyzing the olfactory tracts, located above the cribriform lamina of the ethmoid.(4) In our patient, MRI revealed the absence of olfactory bulbs.

To date, six genes have been implicated: KAL1, FGFR1, FGF8, CHD7, PROKR2 and PROK2. Diagnosis is essentially clinical, as the sensitivity of genetic studies is only 30% (13).

Therapeutic management aims above all to ensure full pubertal development and normal subsequent sexual activity. Gradually increasing the dose of replacement sex steroids (estrogen-progestogen combination in adult women) is a simple way of achieving this goal. Next comes the problem of fertility. (14)

In the literature, 24 pregnancies have been documented in women diagnosed with Kallmann syndrome since 1970. As all individuals with this condition experience hypogonadotropic hypogonadism, ovulation induction is essential for achieving pregnancy. Various ovulation induction methods have been explored for these women, including the use of hMG and hCG, pulsatile gonadotropin-releasing hormone administered via an infusion pump, and recombinant FSH. The success of ovulation induction largely depends on selecting the right gonadotropins and the appropriate method of administration (12). In our case, the patient was treated exclusively with a synthetic form of humanfollicle-stimulating hormone (FSH) for induction.

Conclusion:-

Couple infertility is no longer the sole preserve of women, and men are involved in half of all cases. Male hypofertility has a variety of etiologies, many of which are still unknown. In 30% of cases, they are thought to be linked to a genetic disorder. It is important to know the origin of these infertilities, particularly as the causative genetic factor may be passed on to the offspring.

References:-

1. World HealthOrganization. WHO LaboratoryManual for the Examination of HumanSemen and Sperm-Cervical Mucus Interaction. Cambridge UniversityPress, 1999.
2. Lejeune, H., Brosse, A., Fertipreserve Group, et al. "Fertility in Klinefelter Syndrome." La Presse Médicale, 2014, vol. 43, no 2, pp. 162-170.
3. Lanfranco, F., Kamischke, A., Zitzmann, M., et al. "Klinefelter's Syndrome." The Lancet, 2004, vol. 364, no 9430, pp. 273-283.
4. Smyth, C. M., and Bremner, W. J. "Klinefelter Syndrome." Archives of InternalMedicine, 1998, vol. 158, no 12, pp. 1309-1314.

5. Barr, M. L., and Bertram, E. G. "A Morphological Distinction Between Neurones of the Male and Female, and the Behaviour of the Nucleolar Satellite DuringAcceleratedNucleoproteinSynthesis." Nature, 1949, vol. 163, no 4148, pp. 676-677.
6. Bradbury, J. T., Bunge, R. G., and Boccabella, R. A. "Chromatin Test in Klinefelter's Syndrome." The Journal of ClinicalEndocrinology&Metabolism, 1956, vol. 16, no 5, p. 689.
7. Jacobs, P. A., and Strong, J. A. "A Case of HumanIntersexualityHaving a Possible XXY Sex-DeterminingMechanism." Nature, 1959, vol. 183, no 4657, pp. 302-303.
8. Mascarenhas, M. N., Flaxman, S. R., Boerma, T., et al. "National, Regional, and Global Trends in InfertilityPrevalenceSince 1990: A SystematicAnalysis of 277 HealthSurveys." PLoSMedicine, 2012, vol. 9, no 12, p. e1001356.
9. Smith, S., Pfeifer, S. M., and Collins, J. A. "Diagnosis and Management of FemaleInfertility." JAMA, 2003, vol. 290, no 13, pp. 1767-1770.
10. Opoko, A. P., Yassine, A., and Gaouzi, A. "Jacob's Syndrome and SexualDevelopmentAnomaly: A Case Report." Annales d'Endocrinologie, Elsevier Masson, 2015, p. 502.
11. May-Panloup, P., Malinge, M. C., Larget-Piet, L., et al. "Genetic Causes of Male Infertility and Assisted Reproductive Technologies." Gynécologie Obstétrique & Fertilité, 2001, vol. 29, no 9, pp. 583-593.
12. Nakagawa, K., Iwasaki, W., Sato, M., et al. "SuccessfulPregnancyAchieved by Ovulation Induction Using a HumanMenopausalGonadotropinLow-Dose Step-Up Protocol in an Infertile Patient withKallmann's Syndrome." Journal of Obstetrics and GynaecologyResearch, 2005, vol. 31, no 2, pp. 140-143.
13. Ennazk, L., El Mghari, G., and El Ansari, N. "Kallmann Syndrome in Women: A Case Report." Annales d'Endocrinologie, Elsevier Masson, 2015, p. 408.
14. Heraud, M. H., Grenier, N., Cabry, R., et al. "Management of Ovarian Stimulation in Kallmann-De Morsier Syndrome: The Role of LH." Gynecologie, Obstetrique&Fertilite, 2007, vol. 35, no 6, pp. 548-555.