Genetic Infertility: Exploring Six Rare Cases

ABSTRACT:

Infertility is a complex and heterogeneous disorder influenced by many biological factors, which can affect men, women or both partners. In 2010, the World Health Organization (WHO) estimated that 48.5 million couples worldwide were infertile, with an increasing prevalence due to a growing global population (8). Genetic causes of infertility are suspected in 30% of cases (9). We report one case of Jacob's syndrome, four cases of klinefelter's syndrome, and one case of de Morsier kallmann syndrome.

INTRODUCTION:

Approximately 10-15% of couples experience infertility and male factors contribute to half of these cases. It was usually thought that infertility cannot be transmitted, but accumulating evidence indicates that many cases are indeed caused by genetic defects, some inherited.

KEYWORDS: Genetic infertility;Klinefelter syndrome;Jacob's syndrome; Kallmann-de Morsier syndrome; Azoospermia.

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 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:

According to the WHO (World Health Organization), infertility is defined as the inability of a couple to procreate after two years of unprotected sexual intercourse (1).

-Klinefelter syndrome:

In 1942, Klinefelter, Reifenstein and albright described Klinefelter's syndrome as the association of small, firm testes with hyalinized seminiferous tubules, gynecomastia, elevated gonadotropins and azoospermia. It is one of the most frequent chromosomal anomalies, with a prevalence of around 1/660 male births (2). It is the most common genetic cause of hypogonadism and infertility in men; 11% of patients with azoospermia have Klinefelter syndrome (3).
In 1949, Barr and Bertram discovered a mass of dense chromatin, later called sex chromatin or Barr bodies, in the nuclei of nerve cells in female but not male cats. The discovery that Barr bodies are present in somatic cell nuclei of female but not male human tissue led to the use of stained buccal mucosal cell smears to determine whether the genetic sex of an infant, determined by the presence or absence of a Barr body (presence indicates female sex),

corresponded to the phenotypic sex (5). In 1956, 2 groups of researchers described 7 KS patients using the results of buccal smears which demonstrated Barr bodies (6). In 1959,Jacobs, who discovered that one KS patient had 47 chromosomes, including an extra X chromosome (the 47,XXY karyotype), established that the Barr body observed in KS represents an extra X chromosome (7).
Treatment consists of testosterone replacement therapy to correct the androgen deficiency and ensure patients achieve appropriate virilization. This therapy also has positive effects on mood and self-esteem, and has been shown to 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 in women with confirmed Kallmann syndrome have been reported since 1970. As all women with this syndrome have hypogonadotropic hypogonadism, ovulation induction is necessary to achieve pregnancy, and various methods of ovulation induction have been tried for women with this syndrome, using either hMG and hCG, pulsatile gonadotropin-releasing hormone, by means of an infusion pump, or recombinant FSH. The key to successful ovulation induction lies in the choice of appropriate gonadotropins and the method of administration (12). Our patient was stimulated solely by an inductive treatment based on a synthetic version of human follicle-stimulating hormone (FSH).

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.

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