Obstructive and Non-Obstructive Azoospermia

Subjects: Andrology
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Azoospermia (no sperm in ejaculate), a severe form of male infertility, affects around 1% of men globally. It may be caused by many factors, including blockage of the reproductive tract, hormonal disbalances, ejaculation problems or issues with spermatogenic epithelium or testicular function.

spermatozoa azoospermia sperm isolation sperm analyses

1. Introduction

Azoospermia (no sperm in ejaculate), a severe form of male infertility, affects around 1% of men globally. It may be caused by many factors, including blockage of the reproductive tract, hormonal disbalances, ejaculation problems or issues with spermatogenic epithelium or testicular function. Treatment of azoospermia strongly depends on the cause. If live sperm are produced, they can be retrieved from the testes, epididymis or vas deferens for further IVF therapy (most often for the intracytoplasmic sperm injection method). Three types of azoospermia are described—pre-testicular, testicular and post-testicular.

(a) Pre-testicular azoospermia includes cases of congenital, acquired and idiopathic hypogonadotropic hypogonadism or secondary testicular failure. This is a state when only a small or zero amount of sex hormones is produced due to a disruption of the hypothalamic–pituitary axis. It is associated with poor nutrition, the use of medications (narcotics, chemotherapies), pituitary tumors, trauma or low testosterone (hypogonadism). Therapy of such conditions is possible using hormonal substitution.

(b) Testicular azoospermia is caused by disorders in the development of testicular tissue. The disorders can be congenital (undescended testicles, Klinefelter’s syndrome, Sertoli cell-only syndrome), caused by two genetic errors: chromosomal abnormalities or deletions in the Y chromosome. Acquired causes are mainly infections, gonadotoxic chemicals, cancer, testicular trauma or gonadotoxic therapy. It can also be associated with varicocele or a low level of testosterone.

(c) Post-testicular azoospermia caused by post-testicular abnormalities is usually commonly treatable. The most frequent cause of post-testicular azoospermia is an obstruction in the genital tract (obstructive azoospermia—OA). In patients with cystic fibrosis, CBAVD (congenital bilateral absence of vas deference) is present. The most frequent OA is epididymal obstruction (EO) caused by infection (chlamydia, trichomonas, mycoplasma,

ureoplasma, adenovirus, etc.), iatrogenic, traumatic or idiopathic causes. This form of azoospermia can be caused by retrograde ejaculation brought on by surgical procedures or antipsychotic or antidepressants drugs.

Many causes of azoospermia are curable and fertility can be restored. Men with OA who undergo the semen collection procedure using some of the sperm isolation methods have a high chance of successful collection in more than 90% of cases. Men with non-obstructive azoospermia (NOA) are usually diagnosed with a serious damage to the spermatogenesis itself. In such cases, only very small or no areas of testicular tissue with functional spermatogenesis are preserved. From men with NOA, semen is usually collected by biopsy (sometimes repeated); however, it is successful only in about 30% of cases. The remaining 70% of men with NOA can be subjected to unnecessary repeated biopsies which are often ineffective and may lead to a temporary decrease in serum testosterone, to testicular atrophy, or hypogonadism [1].

2. Obstructive and Non-Obstructive Azoospermia

The OA covers more than 40% of all the cases of azoospermia. It is a condition in which normal endocrine and exocrine functions are preserved and sperm cells are produced in testicles, but they are not present in the ejaculate. The absence of spermatozoa in the ejaculate is caused by obstruction in the genital tract, which can be congenital or acquired. Obstruction can occur on the level of the rete testis, in the efferent ducts, in the epididymis or vas deferens [2].

Congenital OA can appear due to bilateral agenesis of vas deferens, which often occurs in patients with cystic fibrosis as a result of CTFR gene mutation [3]. A correct function of the CTFR protein is essential for prenatal luminization of vas deferens. Mutation of the CTFR disrupts the function of the chloride channel that regulates the concentration of chlorides and water in the lumen of the exocrine glands. The CTFR gene is highly expressed in the cells of epididymis, vas deferens and seminal vesicles, and therefore its mutations affect maturation and transport of spermatozoa. The organs that originate from the Wolf's duct then produce viscous mucus. This leads to obstruction and degeneration of the vas deferens as early as in fetal development.

Epididymides and seminal vesicles are often rudimentary or absent altogether. Degeneration of vas deferens occurs after the 12–18th week of pregnancy [4]. Causes of acquired OA can be infections, trauma, iatrogenic injury or idiopathic epididymal obstruction [5].

While some of these conditions are curable, in most cases, semen must be collected directly from testes or epididymis and subsequent fertilization of oocyte must be performed by intracytoplasmic sperm injection (ICSI).

Approximately 60% of azoospermia cases are NOA, which is defined as the impossibility of sperm production in testicular tissue. It is thus a more serious form of azoospermia. NOA is further categorized into three main subtypes, hypospermatogenesis, maturation arrest and Sertoli cell-only syndrome:

- Hypospermatogenesis is defined as a condition in which all developmental stages of germinal cells are present in testes up to late spermatids, but their production is decreased [6].

- Maturation arrest is a condition in which the activation of androgen receptor on Sertoli cells is disrupted and, subsequently, the development of spermatozoa is ceased on the level of spermatocyte, and thus maturation of the germinal cells is not completed [7][8].

- Sertoli cell-only syndrome describes a state when germinal cells are totally absent. Only Sertoli cells are present in the testicular tissue, filling the seminiferous tubules [9].

Most cases in which biopsy is not effective are represented by Sertoli cell-only syndrome and maturation arrest.

NOA is the reason for infertility in 10% of sterile men [10]. A genetic cause is found in 21–29% of them. The main genetic causes of this condition are chromosomal abnormalities (Klinefelter syndrome) and Y-microdeletions [11].

Klinefelter syndrome is characterized by the presence of an extra X chromosome, with karyotype 47, XXY, found in 80–90% of the patients with Klinefelter syndrome. In the remaining 10–20%, a higher-grade aneuploidy occurs, such as 48, XXXY, 49, XXXXY, 48, XXYY variants or 47, XXY/46, XY mosaic [12]. In patients with Klinefelter syndrome, germinal and Sertoli cells degenerate during puberty, together with hyperplasia of Leydig cells and fibrotization of the interstitium. It is rare that spermatogenesis can be preserved in the seminiferous tubules.

With regard to the high prevalence of genetic abnormalities in men with NOA, it is recommended to perform a screening of karyotype abnormalities and Y-microdeletions. Despite the progress in analysis of Genetic causes of NOA, there are still 50–80% of cases labelled as idiopathic azoospermia [13].

However, NOA can also be caused by external factors, such as varicocele with enlarged plexus of testicular veins, which disables proper blood flow and can lead to overheating and oxidative stress to germinal epithelium [14][15]. Other causes can be endocrine disorders, foreign substances, cryptorchidism, viral diseases (mumps, HPV), testicular failure or gonadotoxins [15][16].

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2022, 4, 782915.

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