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CASUISTRY

AZF gene microdeletions: Case series and literature review☆

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KEYWORDS
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Abstract

Objective: Approximately 10% of patients with non-obstructive azoospermia and 5% with non-obstructive severe oligozoospermia carry AZF region microdeletions (AZoospermic Factor) in the Y chromosome. The aim of this study is to analyze the clinical and pathological findings in this group of patients and compare them with the previous evidence.
Materials and methods: Retrospective study of 11 patients with diagnosis of azoospermia or oligozoospermia was performed and found the presence of AZFa, AZFb, and AZFc microdeletions or any combination of them.
Results: Microdeletions of AZFc region were found in 45% of cases, AZFa in 33% and a 10% showed a deletion of the three regions (a, b and c). 91% of them demonstrated azoospermia with low testicular volume in 62.5% cases.
Conclusion: Microdeletions of AZF regions are associated with azoospermia and a low expectation of sperm retrieval in testicular biopsy. On the other hand, they seem not to be related with significant modifications on the hormone profile.

PALABRAS CLAVE
Azoospermic factor;
Microdeleción Y;
Azoospermia;
Infertilidad primaria;
Genética

Microdeleciones del gen AZF: serie de casos y revisión de la literatura

Resumen

Objetivo: Aproximadamente un 10% de los pacientes con azoospermia no obstructiva y un 5% de pacientes con oligozoospermia severa presentan microdeleciones en las regiones *azoospermic factor* (AZF) del cromosoma Y. El objetivo principal de este estudio es analizar las características clínicas y patológicas de estos pacientes y compararlos con la literatura previa.
Material y métodos: Estudio retrospectivo de 11 pacientes con diagnóstico de azoospermia u oligozoospermia y presencia de microdeleciones AZFa, AZFb, AZFc o sus combinaciones.
Resultados: La microdeleción en la región AZFc apareció en un 45% de pacientes, AZFa en el 33% y un 10% presentaron mutación en las 3 regiones analizadas (AZFa, b y c). El 91% de los pacientes

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con estas microdeleciones presentaron azoospermia con un volumen testicular disminuido en el 62.5%.
Conclusión: Las microdeleciones de la región AZF se asocian a azoospermia y una baja expectativa de recuperación de espermatozoides en la biopsia testicular, sin alterar significativamente la función hormonal.

Introduction and objective

Microdeletion of the AZF region on the long arm of chromosome Y (Yq11.23) is the second leading cause of male infertility of genetic origin, preceded by Klinefelter syndrome.[1] Although its prevalence in the general population is unknown, approximately 10% of patients with non-obstructive azoospermia and 5% of patients with severe oligozoospermia suffer from it. In some publications, the figure may reach 18% in azoospermic patients.[2]

In 1976 the deletion of certain regions on the Y chromosome in infertile males was first described.[3] It was not until 1995 when the final characterization of three distinct regions (designated a, b, and c) took place.[4,5] In 1997, transcription units that would have a critical role in spermatogenesis, linking AZF regions to the spermatogenic process, were described.[6]

Clinically, the common denominator of the deletion of any of these three regions or their combinations is primary infertility with azoospermia or severe oligozoospermia (<5 million/mL) in the absence of virilization disorders. The most reported alterations in the literature include decreased testicular size and rise in FSH levels.[7] Therefore, the main objective that we propose in this review is to analyze the clinical and pathological features of patients with infertility and microdeletions of AZF in our experience.

Materials and methods

A retrospective study was performed from January 2009 to December 2013 from the database for clinical data in patients with non-obstructive azoospermia or severe oligozoospermia (<5 million/mL). Of the sample of such patients, we selected those who had genetic diagnosis of microdeletion of the AZF region (region a, b, and/or c).

The variables analyzed were age, pH, and semen volume (measured in mL), sperm concentration (million/mL), total motility, FSH, LH, and testosterone. The seminal values are obtained from the samples of fresh semen collected in the andrology laboratory, where microscopic analysis of the most successful sample of at least 2 semen analyses and training by means of swim-up technique were conducted. Hormone parameters were obtained by means of peripheral blood analysis using as reference values those of the laboratory of our center (FSH 2–12.4 mU/mL, LH 1.5–9.3 mU/mL, testosterone 3–10 ng/mL). The collected testicular volume was assessed by means of physical examination of a single andrologist. After obtaining the diagnosis of non-obstructive azoospermia, the karyotype and the microdeletions of chromosome Y are studied from peripheral blood sample using the PCR technique.

After reassessing the set of data obtained, patients with azoospermia are given the possibility of sperm retrieval by means of testicular biopsy. This is done on an outpatient basis under local anesthesia and making three incisions located in the upper, middle, and lower pole of the largest testis. Of each of the incisions, two samples, which are analyzed in situ by biologists from the center with the aim of identifying suitable sperm for intracytoplasmatic sperm injection (ICSI) and cryopreserving them, are taken. One more sample is taken that is sent to pathology for structural analysis.

The samples are processed in microtubes to be used later in ICSI. Through face-to-face or telephone interview, the patient is informed of the intention of the study and, after verbal consent on their part, they are questioned on the assisted reproduction treatment offered and it is performed to the couple. All patients were informed and gave their consent to participate in this study.

Results

The data are collected in Table 1.

The mean age of the patients studied was 36.8 years. 90.9% of patients had azoospermia in the spermiogram. One patient had a concentration of 0.25 million sperms/mL. Progressive motility in the spermiogram was only informed in the non-azoospermic patient and it was 0%. The mean seminal volume and pH were normal (4.3 mL and 8.02, respectively).

Regarding the hormone study, the mean FSH was 16 mU/mL (SD: 8.25), and testosterone 7.1 ng/mL (SD: 2.3). The mean LH was 7 mU/mL (SD: 3.6). 45.5% of the patients had a decreased testicular volume, the same as 45.5% had normal testicular volume. Only one patient had atrophic testicular volume (Fig. 1).

At the genetic level, one patient had an altered karyotype (XY-q) and another one a 46XY/45X mosaicism. The most frequent alteration of the Y chromosome was the microdeletion of the AZFc region with 45.5% (5 patients); 3 patients (27.3%) presented alteration in the AZFa region. There was not a single patient with microdeletion in the AZFb region. Two patients showed complete alteration of the three regions with a normal hormonal study and normal testicular volume; in one patient there was AZFbc combined alteration.

In the 3 patients in whom testicular biopsy was performed, the most frequent pathological finding was the syndrome of Sertoli cells only or Del Castillo syndrome (2 patients with altered AZFc and AZFa, respectively). One patient was diagnosed with maturation arrest. In no case sperm suitable for assisted reproductive therapy could be recovered in practiced testicular biopsy.