Y chromosome microdeletions and alterations of spermatogenesis, patient approach and genetic counseling

Microdélétions du chromosome Y et altérations de la spermatogenèse, approche du patient et conseil génétique

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Abstract

Infertility affects 15% of couples at reproductive age and human male infertility appears frequently idiopathic. The main genetic causes of spermatogenesis defect responsible for non-obstructive azoospermia and severe oligozoospermia are constitutional chromosomal abnormalities and microdeletions in the azoospermia factor region of the Y chromosome. The improvement of the Yq microdeletion screening method gave new insights in the mechanism responsible for the genesis of Yq microdeletions and for the consequences of the management of male infertility and genetic counselling in case of assisted reproductive technology.

Keywords: Male infertility; Non-obstructive azoospermia; Oligozoospermia; Yq microdeletion

Résumé

L’infertilité concerne 15 % des couples en âge de procréer et l’infertilité masculine est le plus souvent idiopathique. Les principales causes génétiques de l’altération de la spermatogenèse conduisant à une azoospermie non obstructive ou une oligozoospermie sévère sont les anomalies chromosomiques constitutionnelles et les microdélétions du chromosome Y intéressant la région AZF (azoospermic factor). L’amélioration des techniques de biologie moléculaire permettant d’identifier les microdélétions du chromosome Y ont apporté un nouvel éclairage sur les mécanismes impliqués dans la genèse de ces anomalies et leurs conséquences pour la prise en charge de l’infertilité masculine et le conseil génétique dans le cadre des techniques d’assistance médicale à la procréation.

Mots clés : Azoospermie non obstructive ; Infertilité masculine ; Microdélétions du chromosome Y ; Oligozoospermie
1. Introduction

Infertility affects 15% of couples at reproductive age and is defined as the failure to conceive after at least one year of regular and unprotected sexual intercourse [1]. About 50% of infertility is of male origin. Several factors have been implicated in spermatogenesis alteration such as endocrinological abnormalities, infections, and environmental condition, exposure to chemotherapy or radiotherapy and genetic defects [2]. However, a cause of infertility cannot be identified in up to half of cases. The main genetic causes of spermatogenesis defect responsible for non-obstructive azoospermia and severe oligozoospermia are constitutional chromosomal abnormalities and microdeletions in the azoospermia factor (AZF) region of the Y chromosome. It has been suggested in the different published studies that around 10% of males with non-obstructive azoospermia and oligozoospermia have interstitial microdeletion on the Y chromosome [2,3].

2. The human Y chromosome

The human Y chromosome consists of a short (Yp) and long (Yq) arms and is subdivided in three regions:

- the two pseudo-autosomal regions, PAR1 and PAR2 located respectively in the terminal part of the short and the long arms of the Y and X chromosomes, the genes of the pseudo-autosomal regions show an autosomal pattern of inheritance, PAR1 is the site of the normal crossing-over between the X and Y chromosomes occurring during the first meiotic division;
- the euchromatic region located between the PAR1 and the proximal part of Yq containing the testis determining factor (TDF) with the gene SRY located in Yp and specific genes involved in spermatogenesis located in Yq;
- the heterochromatic region of the Yq with possible large length variation between individuals [4].

Cytogenetic analysis of structural chromosome abnormalities of the Y chromosome such as deletions, Y-autosome translocations or Yp isochromosome have revealed in infertile males with non-obstructive azoospermia, a common region of deletion systematically located on the euchromatic region of the Y chromosome more specifically on Yq11, suggesting the presence of a factor playing a major role in spermatogenesis regulation, azoospermia factor (AZF) [5].

Cytogenetic and molecular analyses confirmed that deletions of euchromatic part of the Y chromosome long arm occurred generally de novo and lead to severe spermatogenesis impairment responsible for oligozoospermia and non-obstructive azoospermia. The first molecular linear deletion interval maps using Y-specific DNA probes allowed to subdivide 98% of the euchromatic region of Y chromosome located between the pseudo-autosomal and the heterochromatic regions of the Y chromosome, initially into 7 and thereafter into 43 interval deletions, each of these intervals consisted of subintervals (A, B, C, . . .) [6]. AZF was located in the intervals 5 and 6 and deletions in these intervals were critical for the normal process of spermatogenesis. The AZF region was subdivided onto three sub-regions, AZFa, AZFb, and AZFc which are required for normal spermatogenesis [5]. A fourth region, termed AZFd, has been recently proposed between AZFb and AZFc region [7]. Each of these regions included active genes and transcription units related to spermatogenesis but also some genes with no testis specific expression. The Y chromosome long arm has many palindromes or inverted repeats – this particular structure is presumed to cause the microdeletions in AZF region found in some of infertile men – and 300 sequence tagged sites (STS) in the Y chromosome mapped for the above three AZF regions [8,9].

3. Y chromosome microdeletions

Y chromosome microdeletions represent the absence of DNA segments or genes from the functionally active part of the Y chromosome and the sequence tagged site-polymerase chain reaction is considered to be the gold-standard method for the molecular diagnosis of Y chromosomal microdeletions. Yq chromosome microdeletions are frequently associated with the quantitative decrease in the sperm production due to spermatogenesis impairment at different stages. The variability in the phenotype of spermatogenesis impairment due to Yq microdeletion may be explain by the type of microdeletions involving different sub-regions of AZF, the size of the microdeletion, the potential effect of the age of the patient, the variability in the penetrance, the presence of germinal mosaics, the coexistence with other male infertility disorders or environmental factors [10].

The overall frequency of Y chromosome microdeletions varies from 1 to 58% in the different published studies, specifically 15–20% of idiopathic non-obstructive azoospermic men, 7–10% of idiopathic oligozoospermic men (sperm counts lower than 5 million/mL) and 2–3% of the candidates for ICSI. The variations in frequencies could be due to the lack of proper patient selection criteria, different ethnic origins of the studied population, sample size, differences in the study design and different selection of STSs [11,12].

The AZFa sub-region located in the proximal portion of interval 5 is characterized by a low deletion frequency. Complete deletion in AZFa region causes bilateral small-sized testes and Sertoli cell-only syndrome (SCOS). Partial deletion in AZFa with particular involvement of USP9Y gene may lead to maturation arrest at the spermatid stage or oligo-, astheno or oligoasthenozoospermia [13–15].

The AZFb sub-region located in the distal portion of interval 5 and the proximal portion of interval 6. AZFb contains 32 genes and overlaps with AZFc. Therefore, deletion in this sub-region often removes certain genes from the AZFc region such as DAZ1 and DAZ2 and is responsible for meiotic arrest at the primary spermatocyte stage [8,16,17].

The AZFc sub-region (interval 6) contains seven distinct genes families that concerns specifically 23 genes. Deletions in AZFc sub-region combined with deletions in other AZF regions account for 87% of Yq chromosome microdeletions and can explain either 12% of non-obstructive azoospermia or 6% of
severe oligozoospermia. Complete deletion of AZF\textsubscript{c} can occur in a preexisting partial deletion or a complete deletion of a pre-existing normal gene. Complete AZF\textsubscript{c} microdeletion may result in Y chromosome loss and sex reversal, with the potential predisposition of the offspring to the 45,X or 45,X/46,XY karyotype. Partial AZF\textsubscript{c} deletions as a result of recombination between sub-amplicons such as gr/gr, b1/b3 and b2/b3, may be clinically relevant for male infertility by altering the normal spermatogenesis or by reducing fertility in the offspring. Microdeletions of AZF\textsubscript{c} can lead to minor spermatogenesis impairment with possible spontaneous pregnancy and therefore the normal transmission of the microdeletion from father to sons [18,19].

4. Genetic counseling and assisted reproductive technology (ART)

The Yq microdeletion screening should be proposed in non-obstructive azoospermic patients and oligozoospermic patients with a sperm count less than 5 million/mL. In case of non-obstructive azoospermia, Yq microdeletion screening may not only identify the origin of spermatogenesis impairment but may also predict the probability of sperm retrieval after testicular sperm extraction (TESE). Furthermore, considering that sperm count may significantly reduce with age in males presenting Yq microdeletions, sperm cryopreservation should be proposed at the time of Yq microdeletion diagnosis if spermatozoa are present in the ejaculate. Consequently, when ART is performed and if Yq microdeletions are observed, the patients and their partners should be counselled for the risk of transmission of Yq microdeletion to the male progeny and the potential alteration of the spermatogenesis of their offspring. Therefore, the couples should be counselled for the necessity of performing semen analysis after the puberty of their sons, to evaluate the possibility of sperm cryopreservation to prevent spermatogenesis impairment.

5. Conclusion

The improvement in the molecular technology that allows the Yq microdeletion screening has led to a substantial improvement in the management of males presenting severe spermatogenesis previously considered as idiopathic. The Yq microdeletion screening has not only a diagnostic aspect but also a prognostic and preventive value. The patient and his partner should be counselled for the consequences of the Yq microdeletion on the chance of sperm retrieval for ART and on the consequence for the male progeny.

Disclosure of interest

The author declares that she has no conflicts of interest concerning this article.

References