Beyond the clinical classification of azoospermia

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There is an ongoing debate regarding the appropriate classification of azoospermia. This manuscript reviews the rationale for the current classification of azoospermia and how to effect a change if there is a need to do so. The current classification of azoospermia into obstructive and non-obstructive is because azoospermia due to ejaculatory duct dysfunction and hypogonadotrophism are extremely rare. Though the use of clinical protocols (defective spermatogenesis, genital tract obstruction, ejaculatory duct dysfunction, hypogonadotrophism or pre-testicular, testicular and post-testicular) may be useful in selecting patients for appropriate treatment, no study has shown that they provide a better method of classification of azoospermia than the current approach. There is increasing evidence of a genetic basis of male infertility as well as the evidence that men’s fertility potential may be classified genetically. Moreover, genetic disorders may be transmitted to the offspring and their presence in infertile couples may affect treatment outcome. It is therefore useful to explore a genetic classification of azoospermia.

Key words: azoospermia/clinical classification/male infertility/obstructive and non-obstructive/pre- and post-testicular

Introduction

Azoospermia is common among the infertile population. It occurs in 10–20% of men found to have abnormal semen analysis (Stanwell-Smith and Hendry, 1984). Its prevalence is likely to increase in infertility clinics. This is because the management and understanding of azoospermia have improved substantially over the recent years and many men who had received chemotherapy or radiotherapy for childhood and adolescent malignancies now survive into adulthood. In the past, the prognosis was poor for most forms of azoospermia. The advent of intracytoplasmic sperm injection (ICSI) has made it possible to treat most forms of azoospermia. Male infertility had in the past received little attention scientifically because the underlying cause of male infertility was largely unknown, especially for those with defective spermatogenesis. Recent developments in molecular biology techniques have led to the elucidation of the genetic basis of some cases of azoospermia. As the number of men with azoospermia increases so will interest in clarifying various conditions related to azoospermia. This increased interest is shown in a recent article (Sharif, 2000) regarding the appropriate classification of azoospermia. He had argued that the current classification of azoospermia (obstructive and non-obstructive) should be replaced with a clinical protocol (pre-testicular, testicular and post-testicular), which reflects the underlying cause of azoospermia. This report reviews the basis for the current classification of azoospermia and whether it is time to change this classification.

Why is azoospermia classified as obstructive or non-obstructive?

Although azoospermia can be due to genital tract obstruction, defective spermatogenesis, ejaculatory duct dysfunction or hypogonadotrophism, it is currently classified as obstructive and non-obstructive. This is because hypogonadotrophic azoospermia and ejaculatory duct dysfunction are rare causes of azoospermia, accounting for about 2% of azoospermia (Hull et al., 1985). Defective spermatogenesis in 60% and genital tract obstruction in 40% of 102 patients with azoospermia evaluated with testicular biopsy and distal vasography were reported (Matsumiya et al., 1994). None of the patients in this series had ejaculatory dysfunction or hypogonadotrophic hypogonadism. Out of the 96 consecutive patients with azoospermia evaluated at Sheffield, 58% had defective spermatogenesis, 31% genital tract obstruction, 7% had features likely to be associated with retrograde ejaculation and 3% were of endocrine origin (unpublished data).

Most of the endocrine causes of azoospermia have usually been addressed by the medical endocrinologists by the time the patients are ready to have children. The frequency of hypogonadotrophic azoospermia in an infertility clinic is less than 0.5%. The acquired forms of hypogonadotrophic hypogonadism seen in an infertility clinic include radiation therapy and some brain tumours, such as craniopharyngioma and prolactinoma. The main congenital type is Kallmann’s syndrome, which occurs in 1 in 10 000 males at birth. In addition, men with hypogonadotrophic azoospermia, like those with defective spermatogenesis, are usually present with testicular atrophy. However, plasma follicle-stimulating hormone (FSH) concentration is usually low or normal in those with hypogonadotrophic azoospermia.

Azoospermia is also an uncommon presentation of ejaculat-
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Table I. Patient selection for treatment of azoospermia according to the clinical classification of azoospermia

<table>
<thead>
<tr>
<th>Category of azoospermia</th>
<th>Clinical pointers as to the likely predisposing factors of azoospermia</th>
<th>Type of treatment</th>
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<tbody>
<tr>
<td>Obstructive azoospermia</td>
<td>vasectomy, vasectomy reversal, STD, swollen testis, distended epididymis, absence of vasa deferentia, semen pH &lt; 7, presence of sperm agglutinins</td>
<td>MESA, PESA, TESA</td>
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<tr>
<td>Azoospermia due to ejaculatory</td>
<td>low semen volume (&lt; 1 ml), diabetes mellitus, retroperitoneal lymphadenectomy, bladder neck surgery, spinal injury</td>
<td>IUI or IVF with spermatozoa retrieved from alkalinized semen sample</td>
</tr>
<tr>
<td>duct dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azoospermia due to hypogonadotrophism</td>
<td>Kallmann’s syndrome, endocrine disorders, low FSH/LH</td>
<td>gonadotrophins or GnRH pump</td>
</tr>
<tr>
<td>Primary testicular sperm</td>
<td>idiopathic, chemotherapy, radiotherapy, malignant disease, cryptorchidism, orchidopexy, torsion of the testis, mumps orchitis, abnormal karyotype, testicular atrophy (&lt; 12 ml), microdeletions of Y chromosome</td>
<td>TESE</td>
</tr>
<tr>
<td>disorder</td>
<td></td>
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</table>

MESA = microsurgical epididymal sperm aspiration; PESA = percutaneous epididymal sperm aspiration; TESA = testicular sperm aspiration; IUI = intrauterine insemination; IVF = in-vitro fertilization; GnRH = gonadotrophin-releasing hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TESE = testicular sperm extraction.

A number of clinical protocols are already in place for the selection of men with various forms of azoospermia. An example of such a protocol is shown in Table I (Ezeh et al., 1999), which is similar to that proposed by Sharif (2000). One important difference between the two protocols is Sharif’s failure to classify those with idiopathic azoospermia. Men with idiopathic azoospermia constitute an important group of men with azoospermia. Previous reports had demonstrated that this group may constitute up to 48–50% of men with non-obstructive azoospermia (WHO, 1989; Jecquier and Holmes, 1993). However, recent studies suggest that many of the so-called idiopathic azoospermia may have a genetic basis. That is why idiopathic azoospermia has been classified under defective spermatogenesis (testicular disorder) in Table I.

The main advantage of the clinical protocols is that they facilitate the selection of men with various forms of azoospermia for treatment and research. It is important to select appropriate groups of patients before the initiation of treatment. This is because each of these groups of azoospermia has a different treatment modality. For example, although the use of testicular and epididymal spermatozoa for ICSI yield similar outcomes, the later is preferred to the former for men with obstructive azoospermia. This is because it is less tedious to process epididymal than testicular spermatozoa. Epididymal spermatozoa could easily be retrieved with microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA). Where these epididymal spermatozoa are not retrieved because of fibrosis or absence of the epididymis, testicular spermatozoa could easily be

ory duct dysfunction. These patients usually present with low volume ejaculate with oligospermia or aspermia rather than azoospermia. Ejaculatory duct dysfunction may be due to either failure of emission or retrograde ejaculation. Those with failure of emission usually present with aspermia while those with retrograde ejaculation present with low ejaculate volume and oligozoospermia (Jarow, 1998). However, the secretions of the bulbo-urethral gland, which normally comprise a small part of normal semen, may be ejaculated in an antegrade manner separate from the rest of the ejaculate so that the patient may notice small semen which shows azoospermia (Pryor, 1994). Nevertheless, it appears that the prevalence of ejaculatory dysfunction may vary from one clinic to the other. Retrograde ejaculation in 18% of men with azoospermia was reported (Yvette et al., 1994). However, there is a general consensus that defective spermatogenesis and genital tract obstruction are the main causes of azoospermia seen in an infertility clinic.

Are clinical protocols appropriate for the classification of azoospermia?

A number of clinical protocols are already in place for the selection of men with various forms of azoospermia. An example of such a protocol is shown in Table I (Ezeh et al., 1999), which is similar to that proposed by Sharif (2000). One
retrieved using the technique of testicular sperm aspiration (TESA). On the other hand, sperm production is marginal and spermatogenesis is sparsely or focally distributed in men with defective spermatogenesis. Testicular sperm extraction (TESE) using multiple small biopsies or a large single biopsy from each testis is therefore the procedure of choice for testicular sperm retrieval in this group (Friedler et al., 1997; Ezeh et al., 1998). In those with retrograde ejaculation, the treatment modalities range from the use of pharmacological agents to in-vitro fertilization (IVF) or artificial insemination with the husband’s spermatzoa recovered from a post- ejaculatory urine sample. In azoospermia due to hypogonadotropinism, hormone replacement with pulsatile gonadotrophin releasing hormone (GnRH) or gonadotrophins is the initial treatment of choice (Kliesch et al., 1995).

Testicular histology combined with or without surgical exploration of the genital tract is the gold standard for the distinction of defective spermatogenesis from genital tract obstruction as a cause of azoospermia. Those with normal spermatogenesis are presumed to have obstructive azoospermia while hypospermatogenesis, maturation arrest, Sertoli cell only and tubular sclerosis indicate azoospermia due to defective spermatogenesis. However, testicular biopsy has its own limitations in clinical settings. First, the information from testicular histology is not always available at the time of the patients’ initial consultation, making patient selection with such information difficult. Second, testicular biopsy with or without genital tract exploration is invasive, even when performed with percutaneous needle biopsy. For these reasons, patient selection for a specific type of sperm retrieval technique is usually based on a set of clinical parameters, especially the plasma FSH concentration and testicular volume: normal FSH concentration and testicular volume indicate obstructive azoospermia while testicular atrophy and raised FSH indicate defective spermatogenesis. However, these two parameters are usually normal in up to 57% men with maturation arrest histological pattern (Ezeh et al., 1998). The selection of patients on the basis of raised plasma FSH concentration and testicular atrophy alone therefore wrongly excludes many patients with maturation arrest. This observation gave rise to the use of more detailed clinical protocols in deciding which patient should receive which type of sperm retrieval technique or treatment (Ezeh et al., 1999).

A more fundamental question to ask is whether the clinical protocols (Ezeh et al., 1999; Sharif, 2000) provide a better approach to the classification of azoospermia than the current method (obstructive and non-obstructive)? At the moment, there is no prospective study comparing the efficacy of the clinical protocols proposed by Sharif (2000) and Ezeh et al. (1999) and the current classification in reaching the diagnosis of the various types of azoospermia. It is the therefore difficult to choose one classification in favour of the other. There is another limitation of the clinical protocol. Although azoospermia with normal plasma FSH concentration and testicular volume suggests genital tract obstruction, raised plasma FSH concentration does not always exclude genital tract obstruction or vice versa. For example, Hauser et al. (1995) described 21 post-vasectomy patients with significant elevation of plasma FSH concentration, and yet they showed normal spermatogenesis on testicular biopsy and the presence of obstructive lesions in the vas or epididymis on surgical exploration. On the other hand, Hendry et al. (1990) reported the presence of defective spermatogenesis in 35 out of 370 (9.5%) patients with normal FSH thought to have obstructive azoospermia. As Sharif pointed out, difficulties may arise in classifying a man who at one time had a vasectomy but later developed testicular dysfunction due to chemotherapy. Neither his protocol nor that in Table I specifically addressed this mixed pattern of clinical scenario, which is rare. In this type of case, one should go further to look at other clinical patterns such as plasma FSH concentration and testicular size before deciding where the patient should undergo TESA, TESE or MESA. Finally, the factors shown in both protocols for defective spermatogenesis (Table I) or testicular group (Sharif, 2000) are merely the predisposing factors to abnormal sperm production and tell you little about the events at molecular level. There is evidence that some of the genetic abnormalities predisposing to male infertility can be transmitted and that they affect treatment outcome (Patrizio et al., 1993; Koboyashi et al., 1994; Silber et al., 1998). A genetic classification of azoospermia focused on its genetic basis would be useful.

What of a genetic classification of azoospermia?

It has been estimated that genetic abnormalities account for up to 30% of the cases of severe male factor infertility (Kupker et al., 1999), most of which present either as azoospermia or oligoasthenoteratozoospermia. Microdeletion of the distal end of the Y chromosome is present in 13–20% of men with azoospermia or oligoasthenospermia (Reijo et al., 1995; Pryor et al., 1997). This region, also called the AZF (the azoospermia factor) region, contains approximately 5×10⁶ base pairs and has been subdivided into three non-overlapping regions – AZFa, AZFb and AZFc. A number of candidate genes such as DAZ (deleted in azoospermia), the RBM (RNA-binding motif), DBY (dead box on the Y), DFFRY (Drosophila fat–fascet-related Y) and others have been described (Vogt et al., 1998). The most common microdeletions occur in the AZFc region, which carries active copies of DAZ. The relationship between the candidate genes and their respective AZF sites are well-described (Vogt et al., 1998). Abnormalities of the candidate genes for spermatogenesis have also been reported in autosomal chromosomes. For example DAZL1 (DAZ-like), a homologous gene to DAZ, is mapped to chromosome 3 in humans. DAZL1 is not identical to DAZ because it has only one sequence repeat of 24 amino acids compared to DAZ with 7–16 repeats. There have been attempts to classify both fertile and infertile men genetically with regard to their fertility potential. A PCR study of the DNA differences in Japanese men without Y chromosome suggests genital tract obstruction, raised plasma FSH concentration does not always exclude genital tract obstruction or vice versa. For example, Hauser et al. (1995) described 21 post-vasectomy patients with significant elevation of plasma FSH concentration, and yet they showed normal spermatogenesis on testicular biopsy and the presence of obstructive lesions in the vas or epididymis on surgical exploration. On the other hand, Hendry et al. (1990) reported the presence of defective spermatogenesis in 35 out of 370 (9.5%) patients with normal FSH thought to have obstructive azoospermia. As Sharif pointed out, difficulties may arise in classifying a man who at one time had a vasectomy but later developed testicular dysfunction due to chemotherapy. Neither his protocol nor that in Table I specifically addressed this mixed pattern of clinical scenario, which is rare. In this type of case, one should go further to look at other clinical patterns such as plasma FSH concentration and testicular size before deciding where the patient should undergo TESA, TESE or MESA. Finally, the factors shown in both protocols for defective spermatogenesis (Table I) or testicular group (Sharif, 2000) are merely the predisposing factors to abnormal sperm production and tell you little about the events at molecular level. There is evidence that some of the genetic abnormalities predisposing to male infertility can be transmitted and that they affect treatment outcome (Patrizio et al., 1993; Koboyashi et al., 1994; Silber et al., 1998). A genetic classification of azoospermia focused on its genetic basis would be useful.
Reclassification of azoospermia

The current classification of azoospermia into obstructive and non-obstructive is adopted because most men with azoospermia have either defective spermatogenesis or genital tract obstruction. Selection of men with different forms of azoospermia using clinical criteria is not new. Clinical protocols such as the one described in this article or that reported by Sharif (2000) can enhance patient selection for specific treatment or research. That is not to say that these protocols provide a clearer definition of azoospermia and should therefore replace the current classification of azoospermia into obstructive and non-obstructive types because each of the approaches has its own limitations and because no study has shown the superiority of one method over the other. The elucidation of the genetic basis of male infertility is still in its infancy but rapid progress is being made in this direction. There is increasing evidence of a genetic basis of male infertility as well as the evidence that men’s fertility potential may be classified genetically. Moreover, genetic disorders may be transmitted to the offspring and their presence in infertile couples may affect treatment outcome. A classification of azoospermia, which reflects its genetic basis, is therefore a better option to pursue.

References

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