UROLOGYPRACTICE

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Detection and Management of Obstructive Azoospermia

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Abstract

Introduction: Obstructive azoospermia represents a treatable form of male factor infertility. With greater demand for assisted reproductive technologies the general urologist may be tasked with initiating the infertility evaluation and providing counsel for treatment options. In this review we discuss appropriate laboratory, radiographic and genetic testing for the patient with obstructive azoospermia. We also outline surgical treatment options.

Methods: The Medline® database was searched for relevant studies of the evaluation and treatment of men with obstructive azoospermia. Key words included obstructive azoospermia, vasovasostomy, vasoepididymostomy, testicular sperm extraction, sperm aspiration and sperm retrieval.

Results: Most published reports were based on small cohorts followed at single institutions. There were sufficient data to characterize the current state of the art and review the standard of practice.

Conclusions: The initial evaluation of azoospermia is primarily based on differentiating obstructive from nonobstructive etiologies with a substantial reliance on history, physical examination and screening laboratory studies. Various treatment options exist for obstructive azoospermia, including reproductive tract reconstruction (vasovasostomy or vasoepididymostomy) or numerous surgical sperm extraction approaches.

Key Words: testis; infertility, male; azoospermia; ejaculatory ducts; sperm retrieval

Abbreviations and Acronyms

CFTR = cystic fibrosis transmembrane conductance regulator

EDO = ejaculatory duct obstruction

FSH = follicle-stimulating hormone

HPT = hypothalamic-pituitary-testis

ICSI = intracytoplasmic sperm injection

IVF = in vitro fertilization

OA = obstructive azoospermia

PercBx = percutaneous testicular biopsy

PESA = percutaneous epididymal sperm aspiration

SV = seminal vesicle

TESA = testicular sperm aspiration

TRT = testosterone replacement therapy

TRUS = transrectal ultrasound

VE = vasoepididymostomy

VV = vasovasostomy

Azoospermia, which indicates the total absence of sperm in the ejaculate, occurs in up to 15% of men seeking an infertility evaluation.[1] Obstruction at any location along the length of the male reproductive tract may result in azoospermia and it represents the etiology in 40% of this population.[1] OA, once an untreatable form of male factor infertility, now exemplifies a readily treated circumstance due to the emergence of IVF and ICSI.

Potential causal factors of obstruction range from acquired insults to congenital anomalies. A wide variety of treatment options is available depending on the nature of the obstruction. In patients with prior vasectomy the surgeon may consider reconstruction with VV or VE. In individuals in whom reconstruction is not an option surgical sperm extraction can be offered with a high likelihood of success. Multiple techniques have been developed to retrieve sperm, each with a unique set of advantages and disadvantages.

With such complexity it has become even more important for the general urologist to initiate the fertility evaluation, provide patients with accurate prognostic information and ultimately determine whether subspecialty referral is warranted.

Evaluation

A diagnosis of azoospermia is confirmed by 2 semen analyses demonstrating a lack of spermatozoa in the centrifuged specimen. The

Submitted for publication June 14, 2014.

No direct or indirect financial incentive associated with publishing this article.

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2352-0779/15/21-33/0
UROLOGY PRACTICE

http://dx.doi.org/10.1016/j.urpr.2014.08.002
Vol. 2, 33-37, January 2015
Published by Elsevier

initial focus when evaluating azoospermia is to differentiate between obstructive and nonobstructive etiologies. A tenet of OA is that the inherent functions of the testis (spermatogenesis and testosterone production) are preserved. A detailed history and physical examination provide the physician with clues regarding the status of testicular function. The patient interview should also include a reproductive history, explore risk factors for obstruction and address any known female factors. Symptoms should be reviewed to further investigate the health of the HPT axis. Evidence that suggests hypogonadism is typically inconsistent with OA.

Risk factors for obstruction include prior surgery, infection or trauma. Iatrogenic injury is possible during inguinal herniorrhaphy, orchidopexy or hydrocelectomy. Vasectomy is by far the most common cause of vasal obstruction.[1] Of the approximately 600,000 vasectomies performed annually more than 6% of men ultimately desire more children.[2] Epididymitis can also impact duct patency. A thorough history should include assessment of prior sexually transmitted illness and prior exposure to tuberculosis. Bronchiectasis, recurrent sinus infections or recurrent pulmonary infections may indicate an underlying ciliary defect or inspissated secretions. Examples include atypical presentations of cystic fibrosis and primary ciliary dysfunction (formerly Young syndrome).

Physical examination will further guide the clinician in distinguishing an obstructive vs a nonobstructive etiology. The inguinal regions and scrotum should be inspected for surgical scars. Normal testicular volume (greater than 15 ml) is the expected finding in the male with OA. The epididymis and spermatic cord should be carefully palpated. Possible anatomical variants include congenital absence of 1 or both vasa deferentia, which can be present in up to 2% of infertile males.[3] Any absent segment of the excurrent ducts should prompt further genetic testing for mutations in the CFTR gene. Finally, digital rectal examination can be useful to palpate midline cysts or SV fullness, which can each be associated with EDO.[4]

Laboratory and Genetic Testing

Even in the absence of sperm insightful information is provided by semen analysis (Appendix 1). Patients with EDO lack the contribution of the SVs to semen. Thus, these individuals typically produce acidic (pH less than 7.0), low volume (less than 1 ml) samples that lack fructose.[4] Similarly in patients with unilateral or bilateral absence of the vasa deferentia concomitant SV atresia may result in a semen analysis profile comparable to that of EDO.

Serum testing should determine the current state of the HPT axis. FSH and the morning testosterone level will help delineate the function of Sertoli and Leydig cells, respectively. Normal FSH (less than 8.0 U/l) and normal morning testosterone are consistent with an obstructive etiology.[5]

Inability to palpate the vas on 1 or both sides should raise concern for a CFTR mutation. Greater than 97% of men with cystic fibrosis have congenital absence of the vasa deferentia.[6] In those with atypical or mild CFTR mutations an absent vasal segment may represent the only clinical manifestation. Occasionally this disruption occurs in the retroperitoneum with otherwise palpable vasa in the scrotum. These individuals are often identified by semen analysis, given that SV atresia is an associated defect. Any patient with unilateral or bilateral absence of the vas deferens or low volume and acidic semen without findings suggestive of EDO should be offered CFTR testing. As the most common genetic condition in white males, more than 1,700 mutations have been described.[6] Most commercially available screens only test for the common anomalies. Since in some men with rare CFTR mutations screening results are negative, it is recommended that the female partners also be tested. Recognizing possible CFTR mutations may alter the family building plan of the couple, warranting a low threshold for referral to genetic counseling.

Radiographic Assessment

Radiographic studies should be guided by clinical suspicion and are often not required to confirm the OA diagnosis. In the patient with absent unilateral vas deferens or bilateral absent vasa and completely normal CFTR testing one should perform renal ultrasound because embryological defects in wolffian (mesonephric) duct development are associated with renal anomalies.[7] In patients with unilateral absence of the vas the rate of ipsilateral renal agenesis can reach 70%.[8]

TRUS may prove useful when evaluating for suspected EDO. A seminal vesicle diameter of 1.5 cm or greater was suggested to be diagnostic of EDO.[4] Additionally, TRUS can detect midline müllerian cysts that may cause mechanical compression.

Treatment

After a diagnosis of OA has been rendered treatment may fall into reconstructive or sperm retrieval approaches. The decision to pursue reconstruction is based on many factors, including female partner age, female factor infertility, number of desired children and anatomical characteristics of obstruction. If reconstruction is likely to fail or IVF is required due to other reasons, sperm extraction remains a viable option in all OA cases.

Medical Optimization

Before treatment one must be certain that there are no issues that may contribute to compromised sperm production. Consider the individual who underwent prior vasectomy and subsequently showed signs or symptoms of hypogonadism, for which he was prescribed standard TRT. Although serum testosterone increases with TRT, the HPT axis is suppressed. This negative feedback potentially results in decreased spermatogenesis due to decreased FSH. TRT may even induce azoospermia in otherwise healthy males. In this population the sperm concentration typically returns to pretreatment levels by 6 months after the cessation of therapy.[9] TRT should be discontinued before surgical management of OA. The optimal