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REVIEW ARTICLE

Aspermia: A Review of Etiology and Treatment

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Abstract

Aspermia is the complete lack of semen with ejaculation, which is associated with infertility. Many different causes were reported such as infection, congenital disorder, medication, retrograde ejaculation, iatrogenic aspemia, and so on. The main treatments based on these etiologies include anti-infection, discontinuing medication, artificial inseminization, intracytoplasmic sperm injection (ICSI), in vitro fertilization, and reconstructive surgery. Some outcomes were promising even though the case number was limited in most studies. For men whose infertility is linked to genetic conditions, it is very difficult to predict the potential effects on their offspring. It is strongly recommended that assisted reproductive techniques should not be started until genetic screening results.

Keywords

Aspermia, Infertility, Etiology, Treatment

Introduction

Aspermia is the complete lack of semen with ejaculation, due to due to either an inability to transport semen (anejaculation) or to ejaculate in an antegrade direction [1,2], which is associated with infertility. Two major causes of aspermia are retrograde ejaculation, ejaculatory duct obstruction [2-4], and sexual dysfunction [5]. In a 9-year prospective monocentre study on 1737 patients to study the causes of male infertility, the main cause of aspermia was severe sexual dysfunction (71.7% of aspermia patients). Despite of these, there are still many other causes we want to explore. We also want to review the outcome of different treatments.

Etiology

Hormonal level change

Aspermia could be divided into testicular aspermia and obstructive aspermia. Hormonal levels may be impaired in case of spermatogenesis alteration, which is not necessary for some cases of aspermia. In a study of 126 males with aspermia who underwent genitography and biopsy of the testes, a correlation was revealed between the blood follitropine content and the degree of spermatogenesis inhibition in testicular aspermia. Testosterone excreted in the urine and circulating in blood plasma is reduced by more than three times in cases of testicular aspermia, while the plasma estradiol level increases 1.5 times. Obstructive aspermia accounts for 12.7% and testicular aspermia for 87.3% of all cases of aspermia [6].

Infection

Aspermia can be associated with TORCH infection [7], brucellosis [8,9], and tuberculosis [10]. One study was to reveal causal relations between infection of the urino-genital tract by intracellular parasites, the so-called TORCH-infections, and the decrease of spermatogenesis. For observation 182 men of reproductive age (from 22 to 38 years) were selected who had oligozoospermia or aspermia, without any complaints or clinical symptoms indicating infection of the urino-genital tract. Out of those, 51 revealed-aspermia. Examinations were carried out for Chlamydia trachomatis (Ch.t), Herpes simplex virus (HSV), Ureaplasma urealiticum (U.u.), Cytomegalovirus (CMV), and Mycoplasma hominis (M.h.). In the group with oligozoospermia, cases of infections by Chlamydia (41.5%) and Herpes virus (51.3%) were frequent, but Ureaplasma (56, 5%) was more frequent than any infections. Cytomegalovirus occurred in the least number of cases. Similar picture was observed in Group II as well. In Group II spermatogenesis remained

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without any changes [7]. Epididymoorchitis is the most frequent genitourinary complication of brucellosis. In one study, epididymoorchitis was detected in 17 out of 134 (12.7%) male patients with brucellosis. Sperm analysis was performed on 14 patients. Five patients had aspermia and eight had oligospermia [8]. The infection associated aspermia could be caused by mechanical obstruction of the ejaculatory ducts, or the development of anti-sperm antibody [11], without a decrease of spermatogenesis.

Spinal cord injury

Aspermia can be associated with spinal cord injury. The inability to ejaculate, i.e. anejaculation, affects the vast majority of men after spinal cord injury [12]. The aspermia from the spinal cord injury can also be a result of ejaculation dyssynergia [13]. In one study, seminal vesicle aspiration was performed immediately before electroejaculation or penile vibratory stimulation in men with aspermia secondary to spinal cord injury. The large number of senescent sperm within the seminal vesicles appears to be a primary cause of poor sperm quality in spinal cord injured men [14].

Diabetes

In one study, 21 consecutive patients complaining of nonejaculatory intercourse were studied. A juvenile diabetic patient was discovered to have nonemission but not retrograde ejaculation [15]. However, diabetes has been reported in another study to lead to retrograde ejaculation (RE) [16].

Medication

Aspermia can be associated with certain anti-hypertensive medications with sympathicolytic activity such as Guanethidine. Results of studies show that this is probably not due to retrospermia, but rather to an interruption of sperm transport during emission [17]. Aspermia can also be caused by progesterone antagonists such as Mifepristone (RU486) [18], anabolic steroids [19], alpha-adrenergic receptor blocking compound (alpha ABC) (for treatment of chronic non-suppurative prostatitis and benign prostatic hyperplasia with lower urinary tract symptoms) [20], phenoxybenzamine (PBZ) [21], anticoagulant abuse [22], and exposure to EDB (ethylene dibromide) (often in workers in citrus fumigation stations and a warehouse used as a holding site before shipment) [23].

Alcohol

Drinking alcohol can lead to aspermia. One study found that in men who were heavy drinkers had seminiferous tubules filled mostly with spermatids that had undergone degeneration, resulting in aspermia [24]. Impotence, decreased libido, and dysfunctional nervous system are commonly associated with alcoholism, which may contribute to the development of aspermia [24].

Radiation

Aspermia can be associated with radiation, either from cancer treatment or accidental exposure [25-32]. Doses of irradiation greater than 0.35 Gy cause aspermia which may be reversible. The time taken for recovery increases with larger doses, however, with doses in excess of 2 Gy aspermia may be permanent. At high radiation doses (> 20 Gy) Leydig cell function will also be affected [28]. In males, fractionated irradiation of the testes may be more harmful than acute, at least up to total doses of about 600 cGy (rad) [32].

One study concludes with a recommendation of combined chemotherapy and involved field radiation for children who have not fulfilled their growth potential, to achieve high cure rates, while minimizing morbidity [26].

Chemotherapy

Chemotherapy can also contribute to aspermia [30]. Anejaculation or retrograde ejaculation from the chemotherapy may account for the aspermia.

Congenital and developmental disorders

Approximately 13.7% of infertile men with aspermia and 4.6% with oligospermia have a coexistent chromosome abnormality. It could be a deletion in Y chromosome [33-35], breakpoint interruption on the long arm of Chromosome 18 [36], X/autosome translocation [37], 45, X/46, X, r (Y) karyotype [38,39], Klinefelter's syndrome [40,41], cystic fibrosis [42-44], and Sertoli-cell-only syndrome [45,46]. Besides a decrease in spermatogenesis, it is unclear if other mechanisms present for the aspermia.

Klinefelter's syndrome: The incidence of Klinefelter syndrome in the general population is 0.1-0.2%, some 3% among infertile patients, and approximately 11% in patients with aspermia [40]. In one study, the results of an analysis of seminal fluid, chromosomal formula, and testicular tissue performed on 32 men (including 2 prepubertal boys) with Klinefelter's syndrome are presented. Aspermia was noted in 11 cases [41]. In very rare cases, these patients might manifest focal residual of spermatogenesis [40].

Cystic fibrosis: Aspermia caused by absence of the vas deferens is well known in cystic fibrosis. Genetic screening for cystic fibrosis revealed a compound heterozygote for CFTR mutations delta F 508 and R 117 H [42]. In one study, delayed menarche in five of seven female patients and infertility in the asymptomatic male patient (two of whom were found to have aspermia) could have led to earlier diagnosis. Teenagers and young adults with long-standing pulmonary or digestive symptoms, unexplained cirrhosis, aspermia, or a sibling with cystic fibrosis should be sweat-tested by pilocarpine iontophoresis [43]. At least half cystic fibrosis patients now reach adulthood. One study reported on 61 patients over 18 years of age who had a clinical

picture of cystic fibrosis at the time of diagnosis. Semen analysis in five men revealed aspermia [44].

Serotoli syndrome: The Sertoli-cell-only syndrome is characterized histologically by complete loss of the germinal epithelium in testicular tubules, and clinically by aspermia, i.e., lack of spermatozoa and their earlier stages in the ejaculate [45,46]. One study examined 53 cases of Sertoli-cell-only syndrome out of a series of 2700 testicular biopsies. All 53 patients had aspermia, and no remnants of germ cells were identifiable in the testicular biopsies [45].

Single nucleotide polymorphisms in UBR2 gene: The associations between three single nucleotide polymorphisms (SNPs; rs3749897, rs16895863 and rs373341) of UBR2 gene and idiopathic aspermia or oligospermia were investigated in a study from China by a case-control experiment with 149 fertile and 316 infertile men, including 244 patients with idiopathic aspermia and 72 patients with severe oligospermia. A significant difference between the oligospermia men (oligospermia group) and the fertile men (control group) was observed [47].

Obstructive aspermia

Obstruction of the ejaculatory ducts can be associated with various diseases of the prostatic gland and posterior urethra, it could also from epididymitis [48-52]. In some of the patients with such clinical manifestations, complete or partial compression of the ejaculatory ducts by the inflamed prostate or seminal bulb may be the cause and the disorder may be transitory rather than continuous [51]. In rare cases, the cause can be a giant multilocular prostatic cystadenoma (GMPC) with seminal vesicle fibrous obliteration [50]. In one study, a posterior urethral valve was found to be the cause of accumulation of sperm during ejaculation, with subsequent aspermia and sterility [48].

Iatrogenic aspermia

Retrograde ejaculation is characterized by aspermia or oligospermia and results from an incompetent bladder neck, often due to a dysfunction of the internal sphincter. Retrograde ejaculation causes < 2% of male infertility but is the leading cause of aspermia [53]. The incidence of retrograde ejaculation is increasing due to surgical aggressiveness in pelvic and genital malignancies. Often it follows retroperitoneal lymphadenectomy [54-56]. To reduce the risk of aspermia, a new modality of retroperitoneal lymphadenectomy as a complementary treatment has been proposed for patients with high risk, stage I nonseminomatous testicular tumor. One study investigated 76 patients with stage I nonseminomatous testis tumor (T1-T4, NX, M0) treated by orchiectomy and retroperitoneal lymphadenectomy. Among them, 33 patients underwent unilateral retroperitoneal lymphadenectomy (URL) and 43 selective retroperitoneal lymphadenectomy (SRL). URL consisted in removing the lymph nodes located around the great vessel homolateral to the tumor (aorta or vena cava and iliac vessels), and anterior and posterior to the contralateral great vessel (aorta or vena cava). SRL was performed removing the lymph nodes located anterior and between the great vessels (aorta or vena cava) and laterally to the homolateral great vessel, extending the distal dissection until the level of inferior mesenteric artery. Mean post-operative follow-up time was 96 months. In the SRL group there was only 5% of aspermia versus 79% in the URL group ($p < 0.0001$). Tumor recurrence was observed in only 5 of the 76 patients and was not related to the surgical technique [54]. In another study, 39 patients with a non-seminomatous testicular tumor underwent retroperitoneal lymphadenectomy (RPLND) between 12/90 and 7/93. Twenty-four patients with stage I disease were operated on with a modified nerve-sparing RPLND, while 7 patients with stage IIA and 8 patients with stage IIB had bilateral RPLND. Twelve of fifteen patients with stage IIA and IIB had preservation of their sympathetic postsynaptic fibers. Intraoperative electric stimulation of the fibers resulted in ejaculation in 25/26 patients. Semen analysis revealed 21 patients with necrospermia and maturation arrest, while 3 had aspermia. Antegrade ejaculation was restored after 1.1 months following nerve-sparing RPLND and 7 months following radical RPLND. Ejaculation did not return in one patient. No patient showed relapse. In sum, nerve-sparing RPLND is superior to radical and modified RPLND with regard to preservation of ejaculation without compromising the radicalness of the tumor surgery [56].

Iatrogenic aspermia can be due to vas or epididymal blockage after pull-through procedures for imperforate anus in infancy. In one study, 20 men who had pull-through procedures for imperforate anus in infancy have been evaluated for infertility. Seven had coexisting renal abnormalities, 4 had had recurrent epididymitis, 3 had had bilateral orchidopexies (at age 7 to 12), 2 had spina bifida, and 1 had a pituitary adenoma. Seven had no ejaculate (aspermia). Both vasa were blocked in 5 men. One vas was blocked in another 7 patients who had abnormalities on the contralateral side; three had epididymal blocks after epididymitis [57].

Idiopathic aspermia

Retrograde ejaculation can be brought on by excessive drug use, or as a result of prostate surgery. It can also be caused by alpha blockers. However, retrograde ejaculation can also be idiopathic [55].

Psychogenic aspermia

Apsermia can have psychological origin [58].

Impaired transformation process of sugar

The prostatic fraction of seminal plasma contains components involved in the transformation of fructose into glucose. Aspermia can be related to deficiencies in this transformation process which can\result in deficient prostatic secretion [59].

Increased vasopressin

In 10 healthy but infertile men, semen analysis was correlated with urinary vasopressin levels. Urinary vasopressin was significantly correlated with sperm count and motility. Higher levels of vasopressin were found to be associated with aspermia and oligozoospermia [60].

Treatment

Anti-infection

In cases of epididymoorchitis caused by brucellosis, combined antibiotic therapy for 6-8 weeks led to improvement in sperm quality in most cases. Only three out of 8 patients had permanent oligospermia and only one out of 5 patients had permanent aspermia after the antibiotic therapy [8]. However, when aspermia was caused by TORCH infection, treatment of the infection did not improve spermatogenesis [7]. It is unclear the exact mechanism for the anti-infection treatment leading to aspermia reversal. However, reversing the gonadal damage and clearing anti-sperm antibodies could be the mechanisms [7,8].

Assisted reproduction

The most common techniques for assisting reproduction are artificial inseminization, in vitro fertilization, and intracytoplasmic sperm injection (ICSI). In the study of 20 men with infertility who had pull-through procedures for imperforate anus in infancy, after reconstruction (4), insertion of sperm reservoirs (4), microscopic epididymal sperm aspiration (2), or artificial insemination (1), sperm were retrieved from 9 men (ejaculated by 4) and 2 pregnancies occurred [57].

Bladder washing and intrauterine insemination: Retrograde ejaculation can be treated successfully with inseminations using spermatozoa obtained from urine. In almost 3 years in one study, eight couples who suffered from infertility due to retrograde ejaculation were treated with inseminations with spermatozoa gained from the urine. The urine-semen sample was collected in 100 mL of Hepes medium and 5 mL 1% human albumin (pH 7.4). After centrifuging, the remaining sperm pellet was dispersed on a Percoll gradient, followed by two washing procedures with Ham's F-10 and human albumin 1%, the remaining sample was used for intrauterine insemination. It seems important to collect the urine-semen sample in a buffered medium and to time the insemination on the basis of the luteinizing hormone (LH) surge [53]. The other study collected RE specimens after postcoital urination into a TEST buffer and resuspended the specimens in the Tes-TRIS (TEST)-yolk buffer, facilitating the recovery and reconstitution of RE fit for artificial insemination [16]. Another study used a protocol involving bladder washing. This method resulted in four normal infants in two couples over eight total insemination cycles. They recommended that in vitro fertilization/ICSI should not be the first step in treating the most couples where infertility is the result of RE [55].

***In vitro* fertilization:** Using microsurgical techniques to aspirate sperm from the first segments of the seminal tract by has permitted *in vitro* fertilization of the oocytes of the partners of men with obstructive azoospermia and ejaculation disorders. Sperm can be aspirated from the epididymis in those cases with deferent duct agenesis or other obstructive pathologies, or from the deferent duct if spermatogenesis is unimpaired and there is no epididymal obstruction, but spermatozoa do not reach the ejaculate. One group reported a pregnancy achieved by *in vitro* fertilization using sperm aspirated from the epididymis and another pregnancy achieved using sperm aspirated from the deferent duct of the spouse with aspermia of psychogenic origin. A micropipette was utilized to obtain the sample, which was prepared using the mini-Percoll method [58].

ICSI: Factors that influenced the clinical results of 220 first-attempt ICSI cycles with testicular spermatozoa were evaluated in 107 men with non-obstructive azoospermia, 72 with obstructive azoospermia and 41 with aspermia. In aspermia, the ICSI outcome depends on both male factors (Follicle-stimulating hormone (FSH), Johnsen score, sperm status and motility) and female factors (age, number of injected oocytes) [61].

One retrospective study evaluated the efficiency of testicular biopsy and ICSI in patients with aspermia or non-obstructive azoospermia (NOA) after cancer treatment. Thirty men with a history of cancer, affected by aspermia or NOA and without sperm cryopreserved before cytotoxic treatment underwent testicular sperm extraction (TESE). After TESE, sperm retrieval was positive in 92% of men with aspermia and 58% of men with NOA. In TESE-ICSI patients with NOA a significantly lower proportion of embryos developed to the blastocyst stage than in patients with aspermia and in those after ICSI with frozen-thawed ejaculated sperm. In patients affected by aspermia or NOA after cancer treatment and without sperm cryopreserved before treatment, TESE-ICSI using testicular sperm provides a chance to father a child, even though the miscarriage rate is high [29]. Another study described an unusual association of aspermia and untreatable, chronic testicular pain in a young man who underwent 14 surgical interventions for an imperforate anus. Physical examination and ultrasonography revealed left epididymal and vas enlargement, normal-sized testes, tubular ectasia of the left rete testis and a small intraprostatic paramedian left cyst. Sperm were only found in a 'testicular touch' preparation. The removed testis was immediately opened and most of the testicular lobules were removed, thus allowing the extraction of 25 × 10 (6) sperm, which were cryopreserved. An 8-month follow-up examination documented the complete absence of pain and, during the

next few months, it is planned to use the thawed sperm for ICSI [62]. For aspermia and infertility associated with Klinefelter's syndrome, employing the ICSI method might help a patient to father a child. There is, however an increased risk of such a child being born with a chromosomal aberration [40].

Sympathicomimetic drugs

One case with transport aspermia following retroperitoneal lymphadenectomy was reported, in whom a retrograde ejaculation could be induced after intravenous application of the alpha-sympathomimetic drug midodrin. After masturbation the semen was collected from the bladder and the spermatozoa were inseminated. Immediately after the first instrumental insemination a pregnancy was obtained [63]. A double-blind controlled study was conducted of the effects on semen quality of 4 alpha-adrenergic agents with and without antihistamines in a patient who had failure of emission secondary to retroperitoneal lymphadenectomy for testis cancer. Four days of treatment were consistently more effective than a single dose, especially for sperm motility. A pregnancy resulted [64]. Another study found that this lymphadenectomy-associated aspermia could be reversed with imipramine [65]. Retroperitoneal lymphadenectomy may produce in the majority of patients an irreversible loss of normal ejaculation due to lesion of presacral sympathetic nerve fibers. In a study, 14.3% of the patients were evaluated to have transport aspermia. By application of alpha-sympathicomimetic drugs this could reverse to an antegrade ejaculation. However, fertility was altered strongly because of motility loss of sperm [66]. In yet another study, three patients had retrograde ejaculation. This was corrected by ephedrine sulfate in the two cases which had a neurological cause [15].

Discontinue medication

In one study, 21 consecutive patients complaining of nonejaculatory intercourse were studied. Three patients had retrograde ejaculation. In one of three patients having nonemission, ejaculation was restored after stopping the drug thioridazine [15]. As previously mentioned, aspermia can also occur as a result of using anti-hypertensive drugs. Medications such as guanethidine can cause long-term aspermia and can be replaced by such drugs as methyldopa which does not cause aspermia as frequently [17].

Surgery

Epididymal tubule vasostomy: In one study, 21 patients with aspermia from epididymal blockage were subjected to epididymal tubule vasostomy using microsurgical technique between 1985 and 1994. In the 21 patients 20 showed sperm, and 18 increased sperm numbers over 4 × 10 (7)/ml postoperation. The wives of 12 patients became reproductive. The selection of 3 different anastomotic ways using microsurgical technique could obviously improve curative effect, according to the dilated degree of epididymal tubule. Liquid-passed test of deferential dust was also recommended [67].

Simultaneous unilateral vasal reconstruction and vaso-epididymostomy: Injuries to the spermatic cords, sustained during childhood inguinal hernioplasty, caused unilateral testicular atrophy, multiple bilateral excurrent duct obstruction and aspermia. One study reported that simultaneous unilateral vasal reconstruction and vaso-epididymostomy resulted in satisfactory semen parameters. It is expected that vasal integrity will be maintained after multiple reconstructive procedures at different locations if further injury to the vascular supply of the excurrent duct is avoided [68].

Microsurgical epididymoneostomy: Based upon the experience of microsurgical treatment of 24 patients (45 operations), one study consider epididymitis to be the main cause of obstructive aspermia. Microsurgical epididymoneostomy was performed to restore seminal vas. This method consists of creating an anastomosis between two parts of the ductus epididymis, bypassing its scarred focus, with or without resection of the latter. Twelve such operations were performed in six patients. Follow-up in four of the patients revealed sperm in all cases [52].

Transurethral resection: The examinations confirmed obstructive aspermia with acceptable spermatogenesis in one case. The site of obstruction involved the colliculus seminalis. Transurethral resection of the colliculus was performed. Following a protracted postoperative andrological treatment pregnancy ensued with uncomplicated delivery [69]. In the other 2 studies, 2 cases of aspermic bilateral atresia of the terminal ejaculatory duct are reported. They were treated successfully by transurethral resection of the prostate gland in the area of the ejaculatory ducts [70,51].

Resection of the posterior urethral valve: A posterior urethral valve was found to be the cause of accumulation of sperm during ejaculation, with subsequent aspermia and sterility. Normal ejaculation was restored after section of the valve, and the patient's partner became pregnant [48].

Sex therapy

In one study of 15 patients with anejaculation of various types, sex therapy succeeded in 4 of 7 cases [15].

Spontaneous recovery

In one study, induction of aspermia was found in 10 out of 14 patients who received over 65 rad to the gonad. Recovery of sperm in the semen occurred in 12 patients within 30-80 weeks after start of treatment. The time of recovery may be dose dependent within the range of 19-148 rad [25]. In the other study, 11 patients who received incidental gonadal irradiation during clinical therapy all became aspermic within 8-34 weeks following treatment. The estimated gonadal dose was 118-228 rads. Five of these patients have shown recovery

of spermatogenesis; 3 of these have reached fertilizable concentrations. Recovery of semen sperm was noted at 44-77 weeks following treatment. The other 2 patients were found to have sub-fertile concentrations of semen sperm after 110-176 weeks [71]. The combination of aspermia and obstructive azoospermia in the same infertile man is a very rare entity. In such cases assisted reproduction should be recommended. However, in a report with one case, an early spontaneous pregnancy rendered this unnecessary [72].

Conclusion

So far we have very good understanding for most etiologies of aspermia, and some treatment outcomes were very promising. However, there are as yet insufficient case numbers to determine whether the effects of the treatments are clear-cut. For men whose infertility is linked to genetic conditions, it is very difficult to predict the potential effects on their offspring. It is strongly recommended that assisted reproductive techniques should not be started until genetic screening results.

Conflict of Interests

The author declares that there is no conflict of interest regarding the publication of this paper.

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