Male Idiopathic (Oligo) ± (Astheno) ± (Terato)-Spermia

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9.1 Definition

Male idiopathic (oligo) ± (astheno) ± (terato)-spermia (iOAT) is defined as a defective spermatogenesis of obscure etiology and is regarded as undetectable using common laboratory methods [1]. iOAT can be classified from a clinical point of view as isolated astheno ± teratospermia (no alteration in sperm concentration), moderate iOAT (sperm concentration $<20 \times 10^6$/mL), or severe iOAT (sperm concentration $<5 \times 10^6$/mL) [2].

9.2 Epidemiology

iOAT affects approximately 30 % of infertile men and is one of the most common causes of infertility [1]. It is likely that its prevalence is increasing, in association with the progressive declining sperm count in men today [3].

9.3 Etiology

Descriptions of reputed causes of iOAT have at least two biases. Two patterns whose alterations are linked to male infertility with normal sperm parameters have been described: DNA damage and alterations of polymerase mitochondrial gamma gene (*POLG*) [4–6] (see Chap. 10). The sum of the percentages of patients with different causes of iOAT gave a result much higher than 100 %. This finding implies that the causes overlap, that the primary cause (if any) of iOAT is still unknown, and/or that more than one cause is needed to affect sperm patterns. The most likely hypothesis

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is the first; it has been demonstrated that iOAT sufferers comprise at least two different populations of infertile men [7].

9.3.1 Age

There is evidence that sperm motility declines progressively after age 30 years, although there is less evidence that a similar decline in sperm volume and concentration may also occur in typical presentations [8, 9].

9.3.2 Noninflammatory Functional Alteration in Post-testicular Organs

Low seminal concentration of prostate-specific antigen, zinc, fructose, and prostatic acid phosphatase [10], and low seminal activity of neutral α-glycosidase are linked to isolated asthenospermia in addition to increased viscoelasticity [11] and osmolarity of seminal plasma [12]. Alterations of epididymal methylation of spermatogenesis-specific genes have been suspected to be involved in the etiology of iOAT [13, 14]. Demethylation is critical for gene transcription.

9.3.3 Infective Agents

Chlamydia trachomatis (CT) and adenovirus (AV) infections have been regarded as being associated with iOAT; however, proof regarding the role of asymptomatic CT and/or AV infection in infertility is inconclusive [15, 16].

9.3.4 Genetic Factors

Approximately 10 % of rat genomes are specifically linked to spermatogenesis, and about 200 genes are regarded as critical for germ cell development [17]; this means that several genes might be involved in iOAT etiology. To be considered a key factor for iOAT, a gene must display all of the following characteristics: (1) it should be specifically expressed in the germ cell line, (2) its altered expression should be associated with iOAT; and (3) it should have an essential role in spermatogenesis [18]. Despite this restriction, several genes have been identified as causes of iOAT [19, 20]. (Diaginic) heredity and de novo mutations are the theoretical causes of the bad gene expression [1].

9.3.5 Mitochondrial Alterations

In asthenospermia, both mitochondrial membrane potential [21, 22] and DNA mitochondrial content [23, 24] are impaired.

9.3.6 Subtle Hormonal Alterations

A decreased luteinizing hormone (LH) pulse frequency has been found to occur in iOAT men whose amplitude parallels the severity of the disorder [25].

Molecular variants of LH have been associated with iOAT [26].

IOAT displays a shift toward lower testosterone (T) serum levels, lower calculated T index, and lower T/LH ratio, and a shift toward higher serum LH levels, higher 17-β2-estradiol (E2), and higher E2/T levels [27]. Increased E2 levels are postulated to contribute to the central suppression of gonadotropin production which, in turn, may decrease both T production and spermatogenesis [28]. E2 is derived mainly from the intratesticular and peripheral aromatization of androstenedione and T by aromatase, a product of the CYP19 gene. CYP 19A1 is a single-copy gene located on chromosome15q21.2. Aromatase polymorphisms have been shown to affect various estrogen-dependent diseases in men and women. The most commonly studied aromatase polymorphism is the tetranucleotide Tyrosine-Tyrosine-Tyrosine-Adenine [TTTA] repeat polymorphism [TTTAn] present in intron 4 of the CYP 19A1 gene. This polymorphism is associated with the activity of the aromatase enzyme both in vivo and in vitro [29]. Higher numbers of TTTA repeats (>7 repeats) in the aromatase gene are associated with a negative relationship between obesity and sperm count. The effect of obesity on E2 and sperm count appears to be absent in men with fewer (≤7) repeats [30].

9.3.7 Environmental Pollutants

Environmental pollutants are regarded as capable of deteriorating semen quality. Chapter 16 is specifically dedicated to this aspect.

9.4 Pathogenesis

The aforementioned causes affect spermatogenesis. Impaired spermatogenesis leads to increased reactive oxygen species (ROS) and unbalanced germ cell apoptosis.

9.4.1 Increased ROS

ROS originate from the cellular physiologic metabolism of O_2 in aerobic conditions, and are mainly produced by leukocytes and immature gametes. Immature gametes are common findings in iOAT. ROS are short-lived chemical intermediates containing one or more electrons with unpaired spins. All spermatozoa structures can be attacked and denatured by ROS [1, 31], ultimately resulting in death and/or irreversible damage. Physiologic (low) levels of ROS exert critical function in normal sperm physiology, such as fertilizing ability (acrosome reaction,

hyperactivation, capacitation, and chemotaxis) and sperm motility; whereas increased ROS generation and/or decreased antioxidant capacity leads to the imbalance between oxidation and reduction in living systems, which is called sperm oxidative stress. This condition was widely considered to be a significant contributory factor to sperm DNA damage/apoptosis, lipid peroxidation, and reduced motility, which, in turn, increased the risk of male factor infertility/subfertility and birth defects [31].

9.4.2 Modified Apoptosis

Apoptosis (programmed cell death) is a physiologic mechanism aimed at achieving optimal Sertoli cell/gamete ratio and removing damaged gametes [32]. The range of stimuli that triggers this activity is impressively broad and includes various forms of electromagnetic radiation, environmental toxicants, heavy metals, and chemotherapeutic agents [33–37]. In addition, genetic perturbation of the germ cell line occurs through, for example, overexpression of SPATA17 [38] or androgen-binding protein [39], or deletion of key genes involved in the regulation of spermatogenesis [40–42]. The impression given is that if spermatogenesis is disrupted in any way, the germ cells tend to default to an apoptotic state. The stage of spermatogenesis when apoptosis is induced appears to be predominantly pachytene spermatocytes, and the Fas (fibroblast-associated death receptor)/Fas ligand and caspase systems seems to be the major mediators of this process [34].

9.5 Diagnosis

iOAT is commonly diagnosed by exclusion; the differential diagnosis is presented in Table 9.1.

Table 9.1 Differential diagnosis of male infertility [2]

Reproductive failure mechanism		Methods of diagnosis
Chromosomal	X chromosome disorders	Objective examination, Y microdeletion detection, karyotype screening of cystic fibrosis, hormonal profiles, androgen receptor detection, semen analysis
	Y chromosome disorders	
	Autosomal disorders	
Developmental	Hypospadias	Clinical history, objective examination, semen analysis, scrotal echography
	Ductal obstruction	
	Didymal-epididymal interruption	

Table 9.1 (continued)

Reproductive failure mechanism		Methods of diagnosis
Testicular pathology	Cryptorchidism	Clinical history, objective examination, semen analysis, scrotal echography
	Ectopic testicle	
	Retarded descent	
	(Floating testicle?)	
	Testicular tumors	
	Bilateral atrophy	
	Trauma	
	Testicular torsion	
Genital tract inflammation	Urethritis	Clinical history, objective examination, semen analysis, scrotal echography, urethral swab, urine analysis, sperm and urine cultural analysis
	Prostatitis	
	Epididymitis	
	Orchitis	
Varicocele		Objective examination, scrotal bilateral echo-color Doppler examination, semen analysis
Endocrine	Pituitary disorders	Hormonal profiles
	Hypothalamic disorders	Semen analysis
	Testicle disorders	
	Thyroid disorders	
	Adrenal gland disorders	
Iatrogenic	Surgery	Clinical history, objective examination, semen analysis
	Drugs	
	Radiation	
Sexually related causes	Erectile deficiency	Clinical history, semen analysis
	Disturbed ejaculation	
General diseases	Renal diseases	
	Liver diseases	
	Neurologic diseases	
	Gastrointestinal diseases	
	Hematologic diseases	
	Autoimmune diseases	
	Infectious diseases (AIDS)	
	Psoriasis	
	Sarcoidosis	
	Diabetes	
Idiopathic oligoasthenoteratospermia		Semen analysis, exclusion criteria

9.6 Therapy

Therapy for iOAT is commonly regarded as empiric, because it is not possible in the current outpatient clinical setting to define the exact etiology of the spermatogenetic disorder of each iOAT patient. A number of therapies have been proposed, the most effective of which, according to author's experience and literature review, are reported here. Obviously these therapies might improve the sperm count in the majority of patients but not in all, and these therapies should be intended as symptomatic therapies: i.e., sperm count is improved as long as these therapies are administered, and decrease immediately after their suspension. Therapies should be administered for at least 3 months, because a stem cell requires about 61 days to achieve the final status of mature spermatozoon [43]. A rough therapeutic classification can be compiled on the basis of sperm analysis results.

9.6.1 Isolated (Astheno) ± (Terato)-Spermia

Coenzyme Q10 100 mg twice daily for at least 3 months. Coenzyme Q10 is a lipophilic antioxidant agent and should be administered after meals. Galenic preparations should use lipophilic excipients (e.g., cocoa butter) [44].

9.6.2 Oligo-Astheno-Teratospermia with Sperm Concentration >5 × 106/mL

l-*Carnitine* 1 g twice daily; *acetyl*-l-*carnitine* 500 mg twice daily; *cinnoxicam* 30 mg, one tablet every 4 days after the main meal. These drugs are antioxidant agents [45, 46].

9.6.3 All Degrees of Dyspermia with Serum Follicle-Stimulating Hormone <2 mIU/mL

Intramuscular *recombinant Follicle-Stimulating Hormone* (*FSH*) 100–300 IU every 2 days. FSH stimulates Sertoli cell function and spermatogenesis [47, 48].

9.6.4 All Degrees of Dyspermia with a low (<10) T/E2 Ratio

These dyspermias have exhibited an increased sperm count after *letrozole* (2.5 mg/day) and/or *anastrozole* (1 mg/day) treatment. Nonobstructive azoospermic patients with T/E2 ratio <10 also had their sperm count increased with letrozole and/or anastrozole treatment. Letrozole and anastrozole are members of a novel class of nonsteroidal, hormone-targeting agents used for breast cancer therapy. They reversibly inhibit the aromatase enzyme, which converts the androgen precursors in adipose

tissue to E2. Blocking of estrogen production has been shown to provoke increased gonadotropin and androgen levels in the blood and a parallel E2 decrease, resulting in spermatogenesis stimulation [49, 50].

9.7 Prognosis

Prognosis is difficult to define in these patients, mainly because of the empiric nature of the therapies. However, antioxidant drugs and aromatase inhibitors significantly lower the number of couples that might require treatment with assisted reproduction to achieve a pregnancy [51].

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