Reproductive health aspects in men with idiopathic inflammatory myopathy. A multicenter study

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ABSTRACT

Objective: To evaluate reproductive health of males with idiopathic inflammatory myopathies (IIM), and comparing them with a control group. **Methods:** Demographic data, urologic evaluation (including pubertal parameters and sexual/erectile function), testicular ultrasound, hormone profile, semen analysis, clinical features, and treatment of 25 IIM patients were evaluated. The control group was composed of 25 healthy males. **Results:** Median age of IIM patients was similar to that of the control group (24 versus 27 years, P = 0.566). The frequency of sexual activity, number of partners with spontaneous pregnancies after the onset of the disease, and use of condom were significantly lower in IIM patients than in the control group (60% versus 96%, P = 0.004; 16% versus 60%, P = 0.0031; 40% versus 76%, P = 0.021, respectively). Moreover, the frequency of testicular atrophy (28% versus 4%, P = 0.049), elevated levels of FSH and/or LH (25% versus 0%, P = 0.05), and sperm abnormalities (40% versus 0%, P = 0.0006) were statistically higher in IIM patients than in the control group. Median age of onset of IIM and current age were significantly higher in IIM patients with sexual/erectile dysfunction than in patients without this dysfunction (41 versus 12.5 years, P = 0.014; 46 versus 21 years, P = 0.027, respectively). On the other hand, differences in the age of spermarche, parameters of gonadal function, disease activity, muscle enzymes, and treatment were not observed between IIM patients with or without sexual/erectile dysfunction. **Conclusion:** This is the first study to identify changes in reproductive health and gonadal dysfunction in male IIM patients. Rheumatologists should discuss sexual problems with their patients, counseling them on contraceptive methods.

Keywords: reproductive health, sexual function, sperm, hormone, idiopathic inflammatory myopathy, male.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM), such as dermatomyositis (DM), juvenile dermatomyositis (JDM), and polymyositis (PM), are systemic autoimmune disorders characterized by chronic muscular imflammation and progressive muscular weakness. Clinical and electromyographic characteristics are similar among the different disorders, and muscle biopsy is considered the "gold standard" for the differential diagnosis.[1,2] The annual incidence of IIM ranges from 0.5 to 8.4 cases per one million people, with higher frequency in two age groups (10 to 15 years and 45 to 64 years), affecting more females than males.[1,2]

Received on 04/09/2009. Approved on 09/28/2009. This study was supported by the Research Support Foundation of the State of São Paulo – FAPESP (from the Portuguese) (Grant 05/56482-7 for CAAS), the National Council for Scientific and Technological Development – CNPQ (from the Portuguese; Grants 300248/2008-3 for CAAS and 305468/2006-5 for Eloísa Bonfá) and Federico Foundation (Grant to Eloísa Bonfá). Clovis Artur Almeida da Silva received financial aid from the remaining funds of SBR.

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Since 1960, the survival and prognosis of IIM patients have improved significantly due to the introduction of corticosteroids followed by immunosuppresants.[2] Those aspects reinforce the importance of studies on quality of life, including the assessment of testicular function and reproductive health,[3-6] such as pubertal landmarks, sexual function, and fertility.[3]

Recently, studying parameters of gonadal function in 10 adult males with DM and a control group composed of 10 matched males, without assessing sexual function, we identified a higher frequency of gonadal dysfunction associated with disease activity in those patients when compared to the control group.[6] In systemic lupus erythematosus (SLE), those changes were associated with the use of intravenous cyclophosphamide.[7-10]

Changes in the reproductive health of male adolescents with JDM have also been reported in the literature[4]. However, the literature lacks studies evaluating sexual and/or erectile function in IIM patients using adequately the word infertility, according to the definition of the World Health Organization (WHO). The World Health Organization emphasizes the need to evaluate the couple, and it defines infertility as the absence of conception after a consecutive period of 12 months of sexual activity without contraceptive methods.[11]

Thus, the objective of the present study was to evaluate gonadal function and reproductive health of males with IIM, comparing them with a control group of healthy males, and to establish possible associations among demographic data, parameters of gonadal function and reproductive health, disease activity, muscle enzymes, and treatment in patients with and without sexual and/or erectile dysfunction.

PATIENTS AND METHODS

Patients with IIM and in the control group

Forty consecutive male patients between the ages of 15 and 54 years were selected for this study between January 2006 and January 2008. This represents the entire patient population on regular follow-up at four Rheumatology Services in the city of São Paulo: Pediatric Rheumatology Unit of the Instituto da Criança (ICr) of Hospital das Clínicas (HC) of the Medical School of Universidade de São Paulo (FMUSP), Myopathies Outpatient Clinic of the Rheumatology Department of HC/FMUSP, Pediatric Rheumatology Department of Universidade Federal de São Paulo, and Pediatric Rheumatology Department of Santa Casa de São Paulo. All patients fulfilled Borhan and Peter criteria for the diagnosis of IIM.[12] Patients did not have malignancies associated with IIM.

Exclusion criteria were as follows: hydrocele, hypospadia, cryptorchidism, testicular mumps infection, testicular cancer, orchitis, testicular vasculitis, ureteral dysfunction, history of scrotal or inguinal surgery, diabetes mellitus, current history of alcohol abuse or smoking, and refusal to collect semen samples or incomplete evaluation. Fifteen patients were excluded: eight for refusing to participate in the study, five for incomplete exam evaluation, one due to orchidopexia due to cryptorchidism, and one due to left testicular ectopy. The remaining 25 patients were evaluated (13 JDM, 10 DM, and two PM) and compared to a control group of 25 healthy individuals: 10 adolescents followed-up at the Adolescent Unit of ICr-FMUSP, and 15 adults followed-up at the Urology Division of the Vasectomy Outpatient Clinic of FMUSP. Socio-economic classes were evaluated according to the classification of the Brazilian Association of Market Research Institutes.[13] The study was approved by the Ethics on Research Committee of HC-FMUSP, and patients or, when applicable, legal guardians signed an informed consent.

Reproductive Health Evaluation

History and urologic exam

Evaluations included: demographic data (age at the onset of the disease, duration of IIM, and current age), body mass index (BMI corresponding to body weight in kilograms divided by the square of the height in meters), age of the first ejaculation (spermarche by masturbation, nocturnal ejaculation, or sexual activity), age of the onset of sexual activity, frequency and number of sexual activities in the previous month, pregnant partners, history of sexual or ejaculatory dysfunction [reduced libido, erectile dysfunction, premature ejaculation, absence of orgasm (anorgasmia), and/or complains with one's sex life].[11,14] Infertility was defined as the absence of conception after a period of 12 consecutive months of sexual activity without the use of contraceptive methods.

The study subjects underwent a systematic clinical exam of the genitalia by the same urologist of the Human Reproduction Center of HC-FMUSP, including evaluation of the testicles, epididymides, vas deferens, scrotum, and penis.[11] Sexual characteristics were evaluated according to the pubertal criteria proposed by Tanner, i.e., distribution of pubic hair and characteristics of the genitalia.[15] Testicular volume was measured with a Prader orchidometer, which consists of 12 numbered beads from 1 to 25 mL (1 to 6, 8, 10, 12, 15, 20, and 25 mL).[16] In post-pubertal adolescents and adult males, testicular atrophy was defined as a testicular volume < 12 mL.[17]

Evaluation of Gonadal Function

Testicular Doppler US scan

All patients underwent testicular US scan performed by the same ultrasonographist from the Radiology Department of HC-FMUSP, a specialist in testicular US scan, using a 14-MHz scanner (Logic 9-GE-Milwauke, Wisconsin, USA), who was blinded regarding the analysis of reproductive health and other parameters of gonadal function. Testicular US scan has better accuracy and precision when measuring the size of the testicles than Prader orchidometry.[3] Testicles were measured on the axial and longitudinal planes by obtaining at least two measurements of the width, length, and thickness. The higher measurement of each dimension was recorded and used to calculate testicular volume according to the formula for the volume of ellipsoids (width x length x thickness x 0.52). In post-pubertal adolescents and adult males, testicular atrophy on US scan was defined as a testicular volume < 7 mL.[18]

Hormonal profile and primary hypogonadism

Hormone levels were measured at the beginning of the study at the Medical Investigation Laboratory (LIM 36, from the Portuguese) of the Pediatrics Department of FMUSP. Abnormal results were repeated for confirmation. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone levels were measured by immunofluorescence using DELPHIA® time-resolved fluoroimmunoassay kits (WALLAC Ou, Turku, Finland). Inter- and intra-analysis coefficient of variation were 3.5% and 2.1%, respectively). Normal levels were as follows: FSH (1 – 10.5 IU/l), LH (1 – 8.4 IU/l), and total testosterone (271 – 965 ng/dL). Primary hypogonadism was defined by elevated serum levels of hypophyseal gonadotropins (FSH and/or LH) and decreased levels of total testosterone.[19]

Changes in spermatozoids

Analysis of spermatozoids, following the directives of the WHO,[11,20] were performed by two experienced biomedical technicians from the Human Reproduction Center of HC-FMUSP, who were blinded regarding the other parameters of reproductive health and gonadal function. All study subjects collected two semen samples, by masturbating in a collection room after 48 to 72 hours of sexual abstinence, up to one month after inclusion in the study. After collection, samples were processed within one hour of liquefaction and underwent both manual count and computer-assisted spermatozoid count under 400 x magnification using the HTM-2030 (Hamilton Thorne Research, Beverly, Massachusetts, USA). Each device was scanned to estimate the number of spermatozoids per 1mL field to obtain the approximate spermatozoid count in millions per milliliter of semen. Spermatozoid mortality was determined by the systematic analysis at least five microscopic fields to classify 200 spermatozoids. Their morphology included the evaluation of the head, neck, midpiece, and tail.[11] Oligozoospermia was defined by a sperm concentration < 200 million/mL, astenozoospermia when the motility of spermatozoids was < 50%, teratozoospermia when normal spermatozoid morphology was < 15%, according to the WHO, and oligoastenoteratozoospermia was characterized by changes in all three parameters.[11] Spermatozoid morphology was also evaluated according to Kruger's strict criteria, in which normal morphology < 14% is associated with subfertility.[21]

Anti-spermatozoid antibodies

The presence of anti-spermatozoid antibodies was investigated in the first semen sample at the Human Reproduction Center of HC-FMUSP. The Immunobead test uses reagents containing rabbit immunoglobulins against anti-human spermatozoid antibodies (IgA, IgG, and IgM) (Irvine Scientific, Santa Ana, California, USA). Direct testing with tagged antibodies can detect antibodies bound to the surface of the spermatozoid (head, midpiece, and/or tail). At least 50% of mobile spermatozoids should be coated with tagged antibodies before the test is considered clinically significant.[20] Quality control followed the recommendations of the manufacturer (Irvine Scientific, Santa Ana, California, USA).

Evaluation of IIM Scores, Muscle Enzymes, and Treatment

The visual analogue scale (VAS)[22], ranging from 0 cm (inactive disease) to 10 cm (highest activity) was used for the global disease evaluation by the physician and patient at the time all parameters of reproductive health and gonadal function were assessed, and the following muscle enzymes were measured: creatino kinase (CK), lactate dehydrogenase (LDH), aldolase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Treatment with prednisone, cyclophosphamide, azathioprine, and methotrexate was also evaluated.

Statistical Analysis

Results are presented as medians (variation), for continuous parameters, and numbers (%), for categorical parameters.

Results were compared by the *t* test or Mann-Whitney test, for continuous parameters, to determine the differences between IIM patients and the control group and between two groups of IIM patients: with and without sexual and/or erectile dysfunction. Fisher exact test was used to analyze categorical parameters. Values of $P \leq 0.05$ were considered statistically significant.

RESULTS

Demographic data, body mass index, reproductive health, and gonadal function in males with IIM and in the control group

Current age and BMI were similar in IIM patients and the control group (24 versus 27 years, P = 0.566; 23 versus 21 kg/m^2, P = 0.1459, respectively). All study subjects had complete sexual development according to Tanner criteria, with adult pubic hair down to the medial aspect of the thighs (P5), and size and shape of adult genitalia (G5).[15] Age of spermarche was not statistically different in both groups (13 versus 12 years, P = 0.093). Mulattoes represented 100% of IIM patients and 96% of the control group (P = 1.0). The frequency of social-economic classes B and C was similar in both groups (80% versus 80%, P = 1.0). The first ejaculation noticed on masturbation was also similar in both groups (72% versus 60%, P = 0.551). The use of condoms was statistically lower among IIM patients than in the control group (40% *versus* 76%, P = 0.021).

As for parameters of reproductive health, sexual activity in the previous month was reported by 60% of IIM patients and 96% of the control group, which was statistically significant (P = 0.004). Besides, the percentage of partners with spontaneous pregnancies after the onset of the disease was statistically lower in IIM patients when compared to the control group (16% versus 60%, P = 0.0031). Median duration of the disease of the four patients whose partners had spontaneous pregnancies was seven years (1-10).

The age of the first sexual relationship, number of sexual activities in the previous month, presence of sexual/erectile dysfunction (reduced libido, erectile dysfunction, premature ejaculation, and/or anorgasmia) and dissatisfaction with one's sex life of IIM patients and the control group was not statistically significant (P > 0.05, Table 1).

A relevant aspect of the presence study was the presence of infertility in only one 38-year old IIM patient and in none of the individuals in the control group (P = 1.0). The wife of this IIM patient was evaluated at the Human Reproductive Center of HC-FMUSP; she had anovulatory menstrual cycles, without history of abortion, and all exams recommended for the evaluation of the female of an infertile couple were normal: pelvic US scan and hormones (thyroid, FSH, LH, estradiol, and prolactin). This patient had active disease (physician VAS 3, and patient VAS 4), he had not been treated with cyclophosphamide, and he presented teratozoospermia. He had erectile dysfunction, being instructed to use 25 mg of sildenafil citrate 30 minutes before sex, which normalized the erection. He has been followed-up at the Human Reproductive Center of HC-FMUSP, but his wife has not become pregnant.

As for gonadal function, 40% of IIM patients had spermatozoidal changes [azoospermia (absence of spermatozoids) or teratozoospermia (abnormal morphology) associated with oligozoospermia (low concentration of spermatozoids), and/or astenozoospermia (decreased mobility)] while they were not present in the control group (P = 0.0006). Testicular atrophy, evaluated by Prader orchidometry and increased levels of hypophyseal gonadotropins (FSH and/or LH), were more common in IIM patients than in the control group (28% versus 4%, P = 0.049, and 25% versus 0%, P = 0.05, respectively). However, the incidence of other parameters of gonadal function, i.e., testicular atrophy on the US scan, primary hypogonadism, reduction in total testosterone levels, and presence of anti-spermatozoid antibodies were not significantly different between both groups (P > 0.05, Table 1).

Parameters of reproductive health and gonadal function in IIM patients with and without sexual and/or erectile dysfunction

Three IIM patients (12%) had sexual/erectile dysfunction, while 22 patients (88%) had normal function. One IIM patient with erectile dysfunction and infertility was described previously. The other two patients are described below:

Patient 1 – 46 years old male with the diagnosis of DM for three years (criteria of Bohan & Peter).[12] His first ejaculation was at 12 years of age, and he started his sexual activities at 17 years of age, but he did not report any sexual activities in the previous months. He complained of premature ejaculation without changes in libido, erection, and orgasm. He did not use condoms, and he was dissatisfied with his sex life. When he was 41 years old, his partner had a spontaneous pregnancy. He had left testicular atrophy [Prader orchidometry and testicular US scan (10 mL and 3.4 mL, respectively)]. The serum levels of hormones were as follows: FSH 22.7 IU/l (1-10.5), LH 7.7 IU/l (1-8.4), and total testosterone 296 ng/dL (271-965). Both semen samples showed terato-oligozoospermia, and anti-spermatozoid antibodies were negative. This patient had active disease with physician VAS of

Table 1. Demographic data, body mass index, parameters of reproductive health, and gonadal function in males with idiopathic inflammatory myopathies (IIM) versus the control group

Parameters	IIM (n = 25)	Controls (n = 25)	P
Demographic data and BMI			
Current age, years	24 (15-54)	27 (15-55)	0.566
BMI, kg/m^2	23 (15-38)	21 (18-27)	0.149
Parameters of reproductive health			
Age of spermarche, years	13 (11-18)	12 (11-15)	0.093
Spermarche due to masturbation	18 (72)	15 (60)	0.551
Tanner pubertal stage P5G5	25 (100)	25 (100)	1.0
Age of onset of sexual activity, years	15.7 (13-21)	16 (12-24)	0.944
Sexual activity in the previous month	15 (60)	24 (96)	0.004
Number of sexual relationships in the previous month	4 (0-28)	8 (0-16)	0.139
Partners with spontaneous pregnancies after the onset of IIM	4 (16)	15 (60)	0.0031
Sexual and/or erectile dysfunction	3 (12)	0 (0)	0.235
Decreased libido	1 (4)	0 (0)	1.0
Erectile dysfunction	1 (4)	0 (0)	1.0
Premature ejaculation	2 (8)	0 (0)	0.49
Anorgasmia	2 (8)	0 (0)	0.49
Dissatisfaction with one's sex life	3 (12)	0 (0)	0.235
Use of condoms	10 (40)	19 (76)	0.021
Infertility	1 (4)	0 (0)	1.0
Gonadal function			
Testicular atrophy according to Prader (R and/or L)	7 (28)	1 (4)	0.049
Testicular atrophy according to the US scan (R and/or L)	4 (16)	2 (8)	0.667
Primary hypogonadism	2 (8)	0 (0)	0.49
Total testosterone < 271 ng/dL	5 (25)	1 (4)	0.189
FSH >10.5 UI/L and/ or LH > 8.4 UI/L	5 (25)	0 (0)	0.05
Spermatozoidal changes*	10 (40)	0 (0)	0.0006
Anti-spermatozoid antibodies > 50%	0 (0)	0 (0)	1.0

Results expressed in numbers (%) or median (variation); P = pubic hair; G = genitalia; R = right; L = left; US scan = ultrasound; FSH = follicle-stimulating hormone; LH = luteinizing hormone; *patients with azoospermia (absence of spermatozoids) or teratozoospermia (abnormal spermatozoid morphology) associated with oligozoospermia (low spermatozoid concentration) and/or astenozoospermia (low spermatozoid motility).

5 and patient VAS of 4. The following muscle enzymes were evaluated: CK 420 IU/l (39-308), ALT 28 IU/l (24-49), AST 14 IU/l (10-36), LDH 485 IU/l (240-480), and aldolase 5 IU/l (< 7.6). Treatment for disease control included prednisone (current dose of 15 mg/day and cumulative dose of 5 grams) and azathioprine (current dose 150 mg/day and cumulative dose of 17 grams).

Patient 2 – 38 years old male with the diagnosis of DM for one year (criteria of Bohan and Peter).[12] The first ejaculation was at 16 years of age, and first sexual activity at 17 years of age, without sexual activity in the previous month. He reported decreased libido and anorgasmia, without erectile and ejaculation difficulties. He did not use condoms and he was dissatisfied with his sex life. He did not report pregnancy. He had normal right and left testicular volumes [Prader orchidometry (25/25 mL) and US scan (13/15.7 mL)]. Hormone levels were as follows: FSH 3.9 IU/l, LH 1.2 IU/l, and total testosterone 231 ng/dL. Semen samples showed teratozoospermia, and anti-spermatozoid antibodies were negative. At the time of the evaluation of reproductive health, he had active cutaneous disease (physician VAS 4 and patient VAS 3). Muscle enzymes were normal: CK 68 IU/l, ALT 24 IU/l, AST 19 IU/l, LDH 454 IU/l, and aldolase 4 IU/l. Treatment for DM included prednisone (current dose 15 mg/day and cumulative dose 4.5 grams), and azathioprine (cumulative dose 15 grams).

DISCUSSION

The present multicenter study evaluated simultaneously parameters of reproductive health and testicular function in patients with inflammatory myopathies, demonstrating a reduction in sexual activity and higher frequency of gonadal dysfunction in males with IIM when compared to the control group.

Sexual function refers to the capacity to complete the sexual cycle, which includes interest, desire (libido), erection, ejaculation, orgasm, and satisfaction.[23] In the present study, all those characteristics of sexual function were evaluated through the clinical history, as suggested by the WHO for evaluation of male infertility,[11] without the use of a generic or specific tool of sexual function and/or depression. Dysfunction and reduction of the sexual activity, such as observed in IIM patients in this study, have been described in male populations with chronic rheumatic diseases, especially rheumatoid arthritis,[24] ankylosing spondylitis,[25] and SLE.[26,27] On the other hand, studies evaluating the sexual function of IIM patients are rare, except for reports of pregnancy in females with those disorders.[28-30] In the present study, 12% of the population of patients with myopathy had sexual dysfunction, with a predominance in middle age

men and those whose disease started later in life. In fact, the incidence of global or specific (such as erectile dysfunction, premature ejaculation, anorgasmia, and sexual dissatisfaction) sexual dysfunction increases progressively with age.[31] Sexual dysfunction could also be secondary to disease activity, myalgia, weakness, or muscular contracture, hindering sex, which was not observed in our patients.

Besides, only 40% of male patients with IIM used condoms during routine sexual relationships. Contraceptive guidelines involve the concept of double protection, i.e., protection against pregnancy and sexually transmitted diseases (including acquired immunodeficiency syndrome and human papillomavirus). Therefore, the use of condoms in all sexual relationships should be emphasized when orienting IIM patients regarding contraception.[13,29] As for females, unprotected sex has increased the incidence of pregnancies, as demonstrated in our patients with JDM[29] and by a recent multicenter Brazilian study on juvenile SLE involving 12 Pediatric Rheumatology Services in four states.[32]

It is interesting that both IIM patients and individuals in the control group started their sexual activity early in life (median 15.7 years versus 16 years). This data was similar in two other studies by our group with women with chronic diseases, in which adolescents with SLE and the control group started sexual activities at a similar age (mean of 15.3 years), and the same was observed in adolescents with epilepsy *versus* a control group of matched healthy individuals (median 15 years).[34]

Similarly to menarche in females, spermarche represents an important pubertal landmark in the reproductive capacity of males.[8] The age of the first ejaculation was not delayed in patients with inflammatory myopathies when compared to the control group. This finding was different from that of female patients with SLE whose menarche was delayed one year when compared to a group of healthy Brazilian adolescents.[33,35]

On the evaluation of male gonadal function, the reduction in testicular volume, according to Prader orchidometry, and spermatozoidal changes suggest severe aggression to seminiferous tubules in IIM patients. Besides, the levels of hypophyseal gonadotropins were higher in those patients. In fact, FSH is a marker of the function of the seminiferous epithelium[9-11] and elevated levels suggest testicular lesion, according to what was observed previously by our group in male patients with SLE, reinforcing the need for cryopreservation of the semen, even without prior use of immunosuppresants, such as cyclophosphamide.[9,10] It is also relevant that, despite the testicular dysfunction observed in our study, most patients still had satisfactory sexual function despite the reduced frequency of pregnancy in their partners after the onset of the disease. Another study that evaluated gonadal function based on dysfunction of Sertoli cells will be undertaken. This dysfunction will be evaluated through the hormone inhibin B, produced exclusively by the testicles.

To conclude, reproductive health and gonadal function are compromised in men with IIM. Patient care should include a discussion on sexuality and contraception, prevention of sexually transmissible diseases, teratogenicity of some drugs used in the treatment, as well as awareness of the risks of the disease and medication represent to fertility.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Thelma Suely Okay, for the determination of hormone levels, and Dr. Ulysses Dória-Filho, for his help with the statistical analysis.

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