

Hyposensitization Therapy with Autologous Semen in Two Dutch Caucasian Males: Beneficial Effects in Postorgasmic Illness Syndrome (POIS; Part 2)

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ABSTRACT

Introduction. Postorgasmic illness syndrome (POIS) is a post-ejaculatory complex of local and/or systemic symptoms that nearly always occurs within seconds, minutes, or hours post-masturbation, coitus, or spontaneous ejaculation. Recent data suggest an autoimmunogenic/allergic underlying mechanism.

Aim. To treat males with POIS by hyposensitization with their own semen (autologous semen).

Methods. Two males suffering from POIS, of which one male with coincidental lifelong premature ejaculation (PE) were investigated. Based on their local and systemic symptoms including a positive dermatologic reaction after skin-prick testing with autologous semen, auto-allergy to semen was likely an underlying mechanism. A hyposensitization program was initiated, including multiple subcutaneous (SC) injections with autologous semen, initially at 2 weeks intervals in the first year and gradually at 4 weeks intervals in the second and third year. From initial semen dilutions of 1 on 40,000 and 1 on 20,000, the titers were gradually increased to 1 on 20 and 1 to 280, respectively.

Main Outcome Measures. Evaluation with a dedicated questionnaire about severity of POIS symptoms and specialized interviews on self-perceived intravaginal ejaculation latency times (IELT) before and during the desensitization program.

Results. POIS was confirmed in both subjects, PE was confirmed in one male, and skin-prick tests with autologous semen in both subjects were positive. During the program, gradual reduction of complaints resulted in 60% and 90% amelioration of POIS complaints at 31 and 15 months, respectively, which coincided in one male with a delay of the IELT from 20 seconds at baseline to 10 minutes after 3 years of treatment. The cause of this association with IELT is unknown and remains to be elucidated.

Conclusions. Two males with POIS were successfully treated by hyposensitization with autologous semen, which supports an immunogenic/allergic etiology and underscores the clinical implication for immunological sexual medicine. **Waldinger MD, Meinardi MMHM, and Schweitzer DH. Hyposensitization therapy with autologous semen in two Dutch Caucasian males: Beneficial effects in postorgasmic illness syndrome (POIS) (Part 2). J Sex Med 2011;8:1171–1176.**

Key Words. Postorgasmic Illness Syndrome; Immunoreactions; Allergy; Semen; Premature Ejaculation; Male Orgasm Disorder

Introduction

Postorgasmic unwell being was for the first time reported by our group in 2002. Based on repeatedly occurring local and systemic illness

post-ejaculation in two males, their cluster of postorgasmic illness symptoms was denoted into the medical literature as postorgasmic illness syndrome (POIS) [1]. POIS appears to be relevant since anecdotal similar experiences have been

published [2] and have been currently exchanged on the website of the International Society for Sexual Medicine. Since 2002, our group was able to collect 45 Caucasian males with complaints of POIS, which were in line with five preliminary criteria that we have put forward based on its original description and a small pilot study [1,3]. In a standardized study of this rather large cohort of men, we were able to categorize local and systemic symptoms and to describe symptom frequency in affected men [3]. This categorization led support to the validity of our initial categorization of five preliminary criteria. In short, POIS is characterized by various symptoms like local mucosal manifestations such as nasal congestion and itching eyes and also by systemic features such as a flu-like syndrome with feverishness, muscle tension of the extremities, extreme fatigue, foggy feeling in the head, concentration difficulties, and mood irritability. In general, the various signs and symptoms of POIS are covered by the five preliminary criteria and appear to occur with great variations in symptom intensity and duration. Notably, this symptom complex (nearly) always starts off after ejaculation, most times within 5–30 minutes, often reaching its peak severity at the second day and gradually diminishes within 1–7 days [3]. Obviously, affected males usually try to avoid ejaculating by planning intercourse or by abstaining from sexual activity. Another important finding was that 56% of the cohort reported to have lifelong premature ejaculation (EP) with an intravaginal ejaculation latency time (IELT) of less than 1 minute. The study also showed that 88% of the males had a positive intracutaneous (IC) skin-prick test for autologous semen. Skin-prick test with saline were unanimously negative. Although a limitation of our study is the absence of a skin-prick test with autologous semen in a control group, the combination of local and systemic symptoms together with highly frequent local reactivity against autologous semen suggests an immunogenic/allergic mechanism to be responsible for POIS.

Two POIS affected males will be presented suffering from intolerable post-ejaculatory symptoms. Both individuals disclosed no underlying disorders and had a positive skin-prick test with autologous semen. Based on a hypothesized immunogenic/allergic underlying mechanism, informed consent was obtained to initiate hyposensitization therapy by repeated applications of diluted autologous seminal fluid for a period of 31 and 15 months, respectively. It was argued that hyposensitization could induce immune tolerance

by inducing blocking antibodies in line with a strategy for different atopic constitutions [4].

Materials and Methods

Two males with complaints of POIS, as previously published [3] consented in participating into a hyposensitization program, which included repeated IC injections with diluted samples of autologous semen. One subject was referred by a sexologist and one by his general physician to our Outpatient Department of Neurosexology in The Hague. Informed consent for study participation was obtained by both individuals after explaining that hyposensitization for POIS is unregistered in the Netherlands and discussing potential side effects of the treatment like local infiltration of the skin, systemic reactions, and even anaphylaxis. Both males consented with the study and with anonymous publication of all data, for which written informed consent was provided. According to the regulations of the Hospital Medical Ethical Committee being part of the National Review Board for Human Medical Studies in the Netherlands, official permission for study participation was not required as the study was not a placebo-controlled drug treatment study.

After establishing the diagnosis “POIS” in each male, further examinations were conducted according to a protocol, which included in-depth neuropsychiatric and sexual medical interviewing, laboratory assessments, and a skin-prick test with autologous semen. Moreover, both males were requested to masturbate once and to collect the semen in a container to be stored immediately into a deep freezer.

The diagnosis POIS was established based on five preliminary criteria, which have been put forward by our group to standardize POIS research: (i) one or more of the following symptoms: sensation of a flu-like state, extreme fatigue or exhaustion, weakness of musculature, experiences of feverishness or perspiration, mood disturbances and/or irritability, memory difficulties, concentration problems, incoherent speech, congestion of nose or watery nose, itching eyes; (ii) all symptoms occur immediately (e.g., seconds), soon (e.g., minutes), or within a few hours after ejaculation that is initiated by coitus, and/or masturbation, and/or spontaneously (e.g., during sleep); (iii) symptoms occur always or nearly always, e.g., in more than 90% of ejaculation events; (iv) most of these symptoms last for about 2 to 7 days; and (v) disappear spontaneously.

Protocol Skin-Prick Test

Autologous semen was intracutaneously inoculated at the volar side of the left forearm (diagnostic start dilution 1 on 40,000). Each diagnostic test was compared with saline 0.9%. In case of nonresponse, anergy was excluded by inoculating a positive control containing histamine [5].

The harvested semen samples were defrosted at room temperature and diluted with saline 0.9%. In addition, 0.05 ml of each dilution was IC injected [5].

Skin reactions were interpreted at 15 minutes after IC injection and found to be positive when the diameter of the wheal was >5 mm with local erythema. The following grading system was used: (i) wheal and erythema < 5 mm = negative; (ii) wheal 5–10 mm and erythema of 11–20 mm = 1+; (iii) wheal erythema of 21–30 mm = 2+; (iv) erythema of 31–40 mm = 3+; (v) wheal > 15 mm or pseudopodia and erythema of >40 mm = 4+ [5].

According to protocol, the hyposensitization strategy became intensified by gradually higher concentrations of inoculated autologous semen. Titrations were performed according to local skin reaction postinoculation, aiming at a wheal and flare response of 3+. This score was intentionally maintained for a period of at least 2 years. Practically, concentrations of semen were periodically increased at a score of 2+ or less. Oppositely, in case the score exceeded 3+, semen concentrations were lowered. In case of systemic reactions, semen concentrations were tapered drastically for a few weeks. Each session was planned every 2 weeks for the first year and followed by once a month in the second and third year.

Clinical effects were monitored regularly by a questionnaire about the severity of signs and symptoms of POIS, developed by the first author. This questionnaire included a score from 0–10 (0 equals no complaints and 10 equals the worst POIS attack). The questionnaire included questions like “during the last two weeks, how severe were your complaints of fatigue after ejaculation?” and “how severe were your complaints of having the flu after ejaculation?”

Case A

Mr. A is a 50-year-old married man who has two children. His medical history revealed hay fever since the age of 43. He does not smoke or use drugs. He used to drink alcohol-containing beverages on a daily basis without any allergic or systemic effect. His medical history was unremarkable: no sexually transmitted diseases and no sur-

gical treatments. At the age of 19, he experienced for the first time a number of weird feelings, occurring 5–10 minutes after each coitus or masturbation but also after spontaneous ejaculation while being asleep. He describes these feelings as getting the flu with feelings of fever, weakness, and exhaustion. He also feels depressed and moody with complete loss of initiative. These complaints coincide with severe headache, dysarthric speech, difficulties in thinking, lack of concentration, forgetfulness, and irritability. His head feels foggy during the whole day and he sleeps for about 4 hours in the afternoon. During his sleep, he experiences frightful dreams that occur during his afternoon naps and at night. He also reports that his lips and throat become swollen. Nearly all these symptoms reach peaks at the second day and lasts for about 4 days, at which all symptoms suddenly disappear within a few hours. He does not report any allergy-like complaints from nose or eyes. He could never find a satisfiable explanation for his post-ejaculatory lack of condition since his physical condition in general has been always unremarkable and even strenuous exercise, like jogging, has not any provocative effects. His sexual desire always remained undisturbed with adequate erections. However, since his first sexual encounters at the age of 19, he regularly ejaculates prematurely within 10 seconds after vaginal penetration. Premature ejaculation, however, has never been reason to seek medical treatment. In order to prevent feelings of illness, he has decided to avoid sexual activity as much as possible. Coitus—if taken place—is usually planned at Fridays to be able to sleep afterwards on Saturday and Sunday.

Based on this history, Mr. A was clinically diagnosed to have a combination of POIS and lifelong premature ejaculation. Routine laboratory and hormonal assessments were normal. Total serum IgE: 53 kU/L (normal < 100 kU/L). Since his flu-like symptoms including swollen lips that occurred post-ejaculation were similar to an allergic hyper-reactivity, he consented in continuing his diagnostic work with a skin-prick test with a diluted sample of his own semen. The inoculation (titer: 1 on 40,000) disclosed a wheal and flare reaction grade 4+, and was associated with the induction of mild POIS complaints.

Based on the hypothesized concept of an underlying allergic diathesis of POIS, he consented in a hyposensitization program in October 2007. His consent included fully acceptance of local and systemic side effects due to treatment including ana-

phylaxis and acute urticaria. Initially, dilutions of 1 on 40,000 were applied and titers were gradually increased to 1 on 20 during a period of 31 months. Remarkably, POIS symptoms attenuated gradually over time, achieving a significant reduction of complaints at 48 hours post-ejaculation. A milestone was reached at 8 months with dilutions of 1 on 6 and at 14 months with dilutions of 1 on 3. At one occasion, his wheal and flare response was >3+, which was followed by tapering semen concentrations and gradual re-administration of higher concentrations. In December 2009, he estimated that POIS had disappeared for some 60%, explaining that there was now a complete disappearance of POIS symptoms at 48 hours with only mild symptoms (feeling a bit weird) at 72 hours. On a rating scale, he had a score of 10 before hyposensitization therapy while it became 3.5 after 3 years of treatment. Taken together, his thinking has been greatly improved without difficulties of thinking, memory, and speech. Moreover, there is hardly any fatigue or need to sleep in the afternoon. His sleep at night has become natural and without nightmares. Excitingly, his self-perceived IELT of some 10 seconds normalized to 5 to 10 minutes, for which he was quite contented. All these changes contributed to a better quality of life, both at home and at work.

Case B

Mr. B is a 53-year-old single man. His medical history revealed hay fever since the age of 30. He does not smoke or drink and he does not use drugs. His medical history revealed an appendectomy but was otherwise unremarkable. At the age of 20, he experienced for the first time a sort of illness, which started at approximately 60 minutes post-ejaculation. He describes his feelings as having the flu together with exhaustion. He also reports a number of allergic symptoms like congestion of his nose and itching and burning eyes. In addition, he also suffers from mood swings, stuttering, photophobia, and lowering of his threshold for sounds. He complains from lack of concentration and he isolates himself from other people. Most of his complaints reach a peak at 48 hours post-ejaculation and last for about 5–7 days. His sexual desire is undisturbed with adequate erections and ejaculations. In order to avoid feeling ill, he has decided to abstain from sex as much as possible.

Based on this history, Mr. B was clinically diagnosed to have POIS. Routine laboratory assessments as well as hormonal assessments were normal. Total serum IgE was 10 kU/L

(normal < 100 kU/L). Since his flu-like symptoms including congestion of his nose and itching and burning eyes were similar to an allergic hyperreactivity, he consented in continuing his diagnostic work with a skin-prick test with a diluted sample of his own semen. The inoculation (titer: 1 on 40,000) disclosed a wheal and flare reaction grade 4+.

Based on the hypothesized concept of an underlying allergic diathesis of POIS, he consented in a hyposensitization program in April 2008. His consent included fully acceptance of local and systemic side effects due to the treatment including anaphylaxis and acute urticaria. Initially, dilutions of 1 on 20,000 were applied and titers were gradually increased to 1 on 280 during a period of 15 months. At two occasions (after 3 and 8 months of treatment) his wheal and flare response was >3+, with increased intensity of POIS symptoms post-inoculation, which was followed by tapering semen concentrations and gradual re-administration of higher concentrations. Remarkably, Mr. B reported a gradual but undisputable improvement of his symptoms with nearly complete, e.g., 90%, disappearance of POIS by April 2010. This improvement contributed to a better quality of life.

Discussion

In the current study, we report on two males with post-ejaculatory complaints that are typical for POIS. Based on the combination of these symptoms and the enhanced wheal and flare reactions after inoculating with autologous semen, we have postulated that hyposensitization treatment with auto-semen may diminish POIS symptomatology. Regular hyposensitization treatments in both males resulted in a gradual diminishment of POIS symptoms. According to protocol, the inoculations with autologous serum were adapted to local skin and systemic clinical reactions, but hyposensitizations were never interrupted nor definitely stopped. Both males were highly motivated to start the hyposensitization treatment and remained motivated to continue this treatment, despite some periods of slow symptomatic improvements. Both patients remained extremely eager to continue treatment because both of them perceived gradual improvement over time.

Postorgasmic illness syndrome is a clinical syndrome with local allergy-like and systemic flu-like symptoms, which occurs exclusively after ejaculation. Affected males may often report atopic con-

stitutions but are otherwise healthy. POIS bears a 22.5-fold risk for lifelong PE [3]. An immunogenic/allergic underlying mechanism of POIS appears to be a realistic option, since 88% of the affected males have a positive skin-prick test with diluted autologous semen [3]. To date, immunologic/allergic data in healthy males without POIS and/or lifelong PE have never been published. Nevertheless, the currently reported hyposensitization program, which included two POIS cases, provides more evidence into an immunogenic/allergic hypothesis. Repeated inoculations with autologous semen induced gradual ameliorations of POIS symptoms and had a delaying effect on the IELT.

In 1911, John Freedman and Leonard Noon published an account of a novel treatment for hay fever [6]. Their method of hyposensitization consisted of injecting increasing doses of an extract of pollen subcutaneously until the hypersensitivity reaction was diminished or abolished. Over subsequent decades, hyposensitization established itself as the cornerstone of clinical allergy [4]. The success of hyposensitization is attributed to special antibodies, called blocking antibodies that appear in the serum after treatment and combine preferentially with the allergen. In case of POIS, autologous semen allergic reactivity has been suggested to occur due to repeated close contact during ejaculatory force between seminal peptides and circulating T-lymphocytes [3]. Indeed, previous research have revealed several loci at which the testis-blood-barrier has become disrupted [7–9]. Blocking antibodies may prevent interaction between seminal allergens and T-cells, which are specialized in presenting these antigens to mononuclear cells and macrophages. The flu-like reaction by males with POIS post-ejaculation can be explained by an acute phase reaction, which is characterized by the onset of fever, temporary lymphocyte depletion, and a transient rise of C-reactive protein, interleukin-6, and TNF α [10].

The desensitization program in both our patients had remarkable clinical effects in terms of amelioration of POIS symptoms, but interestingly, it also improved lifelong PE in Mr. A, who reported a gradual improvement of lifelong PE from IELTs of less than 20 seconds towards 10 minutes after 2 years of hyposensitization treatment.

The co-occurrence of lifelong PE in 56% of males with POIS [3] may be related to the low frequency of sexual activity in these men, or may be an epiphenomenon of disturbed urogenital

function. However, its occurrence in POIS may perhaps also be a manifestation of so far unknown immunogenic/allergic pathogenesis of PE. Yet, currently there are no data available on possible interactions between POIS and PE and to our knowledge, there are no reported observations to suggest that PE has an immunogenic/allergic etiology. Scientifically, measurement of IELT has become a reliable and reproducible tool in drug treatment studies for PE [11]. Although Mr. A was known with lifelong PE, the diminishment of PE complaints in Mr. A confirms the likelihood of the secondary nature of PE in this patient affected by POIS but may perhaps also indicate that IELT assessment may serve as surrogate marker in desensitization programs against POIS in men with associated PE.

Close contact between autologous peptides—independently where they originate from—and T-lymphocytes may activate the immune system and repeated exposure may lead to hyperactivity of the immune response with an array of responses. Whether the type of antibody formation in POIS is specific, e.g., against specific peptides from seminal fluid or from disrupted urethral lining cells, or nonspecific and cross-reactive against a protein family remains uncertain. Protein families descend from a common ancestor, which is evolutionary related. Family proteins have similar three-dimensional structures, functions, or structural similarities. Currently, over 60,000 protein families have been defined and the rate of discoveries of new families is constantly growing [12]. In a series of 45 Caucasian males, 26 (58%) males reported some sort of atopic constitution, and indeed, Mr. A and B also complained from hay fever. In case of cross-reactive blocking antibody formation, it may be argued that any anti-allergy desensibilization program like grass pollen may perhaps help to suppress POIS and/or PE symptoms.

Although the current case reports support our hypothesis of an allergic response against autologous semen, there are some limitations that need to be mentioned. In the first place, there are no valid data over the prevalence of POIS and the immunogenic/allergic response of healthy males against their own semen. Secondly, although the skin-prick test has been applied together with a saline control, both case reports have by far no power to proof treatment efficacy as compared to a randomized placebo-controlled clinical trial. Nevertheless, our two cases provide a fascinating clinical challenging hypothesis to study immunology

and allergy in sexual medicine including the therapeutic aspects of desensibilization with autologous semen in patients with POIS. However, for prospective studies and treatment strategies, positive skin-prick tests should be performed in order to get more insight in POIS. One of the fundamental questions in this respect is whether one should increase the dose of autologous semen in case of a negative test. Studies are needed investigating titrations of the initial dilutions in skin-prick test negative individuals.

Notably, hyposensitization treatment should preferably be performed in a well-equipped medical centre, as there is a risk for systemic reaction or anaphylaxis. Moreover, a limitation of hyposensitization is the risk of worsening of allergy symptoms, and the need for booster doses to prevent recurrence of symptoms.

Conclusion

This is the first report of hyposensitization treatment with autologous semen in medical literature. The successful diminishment of POIS complaints in the course of 15 and 31 months of regular injections argues in favor of an autoimmune etiology of POIS. This case report may be a start off to study this concept in males with a complex of local and systemic reactions that repeatedly occurs post-ejaculation. Based on its initial clinical description and a small pilot study, five preliminary diagnostic criteria were proposed for establishing the diagnosis "POIS." Certainly, we need many more cases to be able to prove the effect of a hyposensitization program. Nevertheless, by publishing the first anecdotal clinical experiences of a hyposensitization program, it is our sincere hope to pursue this approach in larger groups and according to evidence-based medicine. Finally, the coincidence of POIS and PE is remarkable and deserves further attention in future POIS treatment strategies.

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