Post-Orgasmic Illness Syndrome: A Review

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ABSTRACT

Introduction: Post-orgasmic illness syndrome (POIS) is a rare but debilitating cluster of postejaculatory symptoms affecting men. It is a chronic disorder manifesting as a constellation of flulike and allergic symptoms within seconds, minutes, or hours after ejaculation. POIS can be followed by mental sequelae such as diminished concentration and irritability. POIS negatively affects the life of patients by limiting sexual encounters, dampening romantic prospects, creating internal struggles to avoid eroticism, and affecting patients' schedules. First described in 2002, the prevalence and incidence of POIS are still unknown owing to a paucity of studies but is likely under-reported. There are approximately 50 cases of POIS in the literature. Despite the debilitating effects of POIS, the pathophysiology of POIS is still not well elucidated.

Aim: To provide an update on the current literature on POIS, provide updated information on the pathophysiology of POIS, and discuss potential management options.

Methods: Comprehensive review of literature pertaining to POIS.

Main Outcome Measures: The symptoms, classification, pathophysiology, diagnostic considerations, and management of POIS were reviewed.

Results: There are 5 preliminary diagnostic criteria for diagnosing this condition. POIS is categorized as primary or secondary. The autoimmune-allergy hypothesis is the most accepted hypothesis explaining the pathogenesis of POIS. A competing hypothesis involves a disorder involving endogenous μ-opioid receptors. Another hypothesis invokes impairment of the cytokine and neuroendocrine responses. There are no known treatment modalities for POIS; patients have been symptomatically treated with antihistamines, selective serotonin reuptake inhibitors, and benzodiazepines. A trial of hyposensitization therapy with autologous semen was successful. A trial of non-steroidal anti-inflammatory medication helped 1 patient described in a single case report, but failed to successfully treat other patients.

Conclusions: POIS is a rare condition that is underdiagnosed and under-reported. Further studies are warranted to investigate the prevalence, pathophysiology, and treatment of this debilitating condition. **Nguyen HMT, Bala A, Gabrielson AT, Hellstrom WJG. Post-Orgasmic Illness Syndrome: A Review. Sex Med Rev 2018;6:11–15.**

Key Words: Post-Orgasmic Illness Syndrome; Ejaculation Disorder

INTRODUCTION

Post-orgasmic illness syndrome (POIS) is a rare cluster of postejaculatory symptoms first described by Waldinger and Schweitzer[1] in 2002. They published a case report of 2 men who exhibited flulike symptoms, such as myalgias, fatigue, and intense warmth, and local allergic signs, such as sore throat, postnasal drip, skin erythema, and a burning sensation in the eyes that occurred shortly after ejaculation. The onset of symptoms in these 2 patients was described as rapid, on the order of seconds to hours after ejaculation. These recurrent symptoms after ejaculation were followed by mental sequela, including diminished concentration and irritability. In general, the symptoms of POIS occurred after ejaculation by intercourse, masturbation, or spontaneously during sleep and persisted for 3 to 7 days.[2]

In an effort to limit the symptomatology, most patients with POIS resort to deceased sexual activity or abstain altogether.[1,3–5] The physical and psychological effects of POIS can significantly affect the quality of life of patients.

The prevalence and incidence of POIS are unknown owing to a paucity of studies. There have been fewer than 50 cases recorded in the literature since POIS was first described.[6,7] The National Institutes of Health Office of Rare Disease Research recognizes POIS as a rare disorder; however, recently there has been an

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Table 1. 5 preliminary diagnostic criteria of post-orgasmic illness syndrome[5]

Criterion	Description
1	≥1 of the following symptoms: sensation of flulike 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, itchyeyes
2	All symptoms occur immediately (eg, seconds), soon (eg, minutes), or within a few hours after ejaculation that is initiated by coitus and/or masturbation and/or spontaneously (eg, during sleep)
3	Symptoms occur always or nearly always (ie, >90% of ejaculation events)
4	Most of these symptoms last for ∼2–7 d
5	Symptoms disappear spontaneously

increasing number of self-reported cases of POIS on internet forums, suggesting that POIS is underdiagnosed and underreported.[6] As the signs and symptoms of POIS become well characterized in the literature, it is expected that more patients will seek evaluation and medical treatment. This undoubtedly will assuage the anxieties and fears of many patients with POIS symptoms, many of whom have been unsuccessfully worked up for psychiatric or factitious somatic symptom disorders.[2]

This review seeks to provide an update on the current literature on POIS. The authors also aim to provide updated information on the pathophysiology of POIS and to discuss potential management options.

CLINICAL PRESENTATION

Using data from a study involving 45 Dutch Caucasian men with POIS, Waldinger et al[5] suggested 5 preliminary diagnostic criteria for assessing the spectrum of this condition. They proposed that the presentation of POIS was highly variable; however, 5 criteria captured the majority of cases (Table 1). Criterion 1 includes at least 1 of the following symptoms: flulike state, extreme fatigue, generalized weakness, fever or perspiration, mood disturbances, problems with memory or concentration, incoherent speech, runny nose or nasal congestion, and itchy eyes. Criterion 2 requires that all symptoms happen within seconds, minutes, or a few hours after ejaculation. Criterion 3 dictates that symptoms occur in more than 90% of ejaculation events. The 4th criterion is that most of these symptoms last 2 to 7 days. The 5th criterion is the spontaneous disappearance of symptoms.

Waldinger et al[5] documented that POIS symptoms start within 30 minutes of ejaculation in 87% of afflicted men. They also noted that although POIS presentation can be variable among patients, especially for the 1st criterion, the symptoms remain relatively constant for individual patients. Waldinger et al further stratified the symptoms in criterion 1 into 7 clusters, as described by the patients' own words. The 7 clusters are listed in Table 2 and include (i) general, (ii) flulike, (iii) head, (iv) eyes, (v) nose, (vi) throat, and (vii) muscle.

In the study by Waldinger et al,[5] of the 33 men (73%) with a partner, the intercourse frequency was 1.04 ± 1.00 times per week, with 3 men abstaining from intercourse. 8 of these 33 men reported an intercourse frequency of once in 2 to 6 months. Of men older than 30 years without a partner, 6 refrained from masturbation or intercourse as much as possible.[5] Similar avoidance of sexual activities has been reported in other cases in the literature.[3,4,6] This finding sheds light on the severe mental and psychosocial burden POIS can place on men affected by this disorder (Figure 1). Patients affected by POIS have lower ejaculation frequency, despite their normal urge to engage in intercourse and intimacy. This leads to internal struggles between enjoying erotic activities and avoiding them for fear of ejaculation and the associated symptoms. Furthermore, because ejaculation can decrease concentration, alertness, and physical capacity, many patients must plan ejaculations ahead of time to avoid inconveniences during everyday activities such as work or study.[2,3,5] Many young men with POIS might be hesitant to seek a romantic partnership owing to fears of stigma and lack of acceptance in abstaining from intercourse.[2] One interesting finding reported by Waldinger et al was that during a POIS

Table 2. 7 clusters of criterion 1 of post-orgasmic illness syndrome[5]

Cluster	Description
1 (general cluster)	Extreme fatigue, exhaustion, palpitations, anomic aphasia, incoherent speech, dysarthria, concentration difficulties, irritability, hyperacusis, photophobia, depressed mood
2 (flulike cluster)	Fever, extreme warmth, perspiration, chills, prodrome, cold intolerance
3 (head cluster)	Headache, fogginess, heaviness in the head
4 (eyes cluster)	Burning, conjunctival injection, blurry vision, eye pain, watery discharge, eye irritation and itchiness
5 (nose cluster)	Nasal congestion, rhinorrhea, sneezing
6 (throat cluster)	Dirty taste in mouth, dry mouth, sore throat, tickling cough, hoarse voice
7 (muscle cluster)	Muscle tension in the back or neck, muscle weakness and pain, heaviness in the legs, muscle stiffness

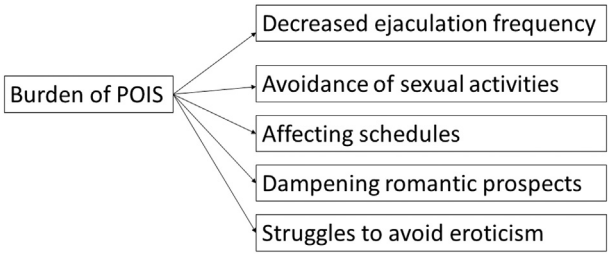

Figure 1. Burdens of POIS in afflicted patients. POIS = post-orgasmic illness syndrome.

"attack," previously healed scars of trauma or surgery and/or a latent illness would exhibit increased sensitivity and pain. This temporary allodynia disappeared concomitantly with the regression of POIS symptoms. This phenomenon could be hypothetically attributed to immunologic mechanisms that are induced during POIS attacks.[2] Of note, 56% of the men included in the study by Waldinger et al[5] reported lifelong premature ejaculation (PE) with an intravaginal ejaculation latency time shorter than 1 minute. Waldinger et al estimated that POIS bears a 22.5-fold risk for lifelong PE. Jiang et al[6] and Shigeta et al[4] also reported lifelong PE in their 2 patients with POIS.

CLASSIFICATION

Based on their study involving 45 Caucasian men, Waldinger et al[5,8] suggested that there were 2 major types of POIS: primary and secondary. Patients with the primary type demonstrate signs of POIS from their very first ejaculation in adolescence. However, patients with the secondary type do not demonstrate signs of POIS until late adulthood. The number of patients in each subtype in the study by Waldinger et al[5] was fairly even: 49% of men had the primary subtype and 51% of men had the secondary subtype. Of the other 4 cases described in the literature, 2 patients had the primary type and 2 other patients had the secondary type.[3,4,6,8]

PATHOPHYSIOLOGY

Given the rarity of POIS in the general population, few studies have explored the pathophysiology of this condition. However, there are several hypotheses on the pathogenesis of POIS. The most accepted hypothesis proposed by Waldinger et al[8] defines POIS as an immunologic phenomenon. They postulated that POIS is an autoimmune or allergic disorder that generates an inflammatory reaction to a substance in the man's seminal fluid. This theory is supported by a study of skin prick test (SPT) reactions of patients with POIS and extremely diluted autologous semen.[5] Harvested semen was diluted to a concentration of 1:40,000, subsequently injected intracutaneously into the volar side of the left forearm, and compared with placebo skin reaction with intracutaneous saline 0.9%. Of the 33 men with POIS who were tested, 88% had a positive SPT reaction to their own semen, whereas none showed a skin reaction to the placebo SPT.[5] Waldinger et al concluded that a patient's type I and type IV allergy to his own semen might act as the main driver of POIS sequela. Because POIS symptoms did not occur during sexual activities without ejaculation, Waldinger et al[5] postulated that POIS also might involve a hyperactive immune response of the mucosal epithelium lining the urinary tract to the seminal fluid. Because of the lack of local genital skin reaction after ejaculation, the occurrence of multiple systemic complaints, and the successes of hyposensitization treatment, they postulated that POIS immunologic reactions occur as a result of repeated close contact during ejaculations between seminal peptides and T lymphocytes.[5] Peptides from disrupted urethral lining cells or autologous seminal peptides in contact with the inner mucosal epithelium of the urethra are subsequently taken up by dendritic cells and then transported to the paracortex of lymph nodes. In the paracortex, naïve T cells interact with seminal fluid antigens, thereby initiating clonal expansion of autoreactive T cells and leading to the putative hypersensitivity reaction.[9] In a subsequent study, Waldinger et al[8] investigated whether hyposensitization with autologous semen would alleviate the symptoms of POIS. 2 patients consented to participate in the hyposensitization program. The hyposensitization protocol involved repeated intracutaneous injections of autologous semen with increased concentrations over time. The 2 patients reported diminished POIS burden after 15 and 31 months of injections.[8] 1 patient also reported significant improvement of his PE as his POIS symptoms decreased.[8] This study further supports the autoimmune-allergic nature of POIS. Limitations of the studies by Waldinger et al include a lack of healthy control men for the autologous semen SPT results and the observational study design. In addition, the case report by Nguyen et al[10] showed that their patient with POIS had positive SPT and intradermal test reactions to his own semen.

Of note, 58% of the cohort in the study by Waldinger et al had many forms of allergies. Similarly, Jiang et al[6] and Shigeta et al[4] reported an atopic constitution in their 2 patients. However, the mean serum total immunoglobulin E (IgE) in men without atopy in the study by Waldinger et al[5] was 27 kU/L (range = 6–78), suggesting that IgE is normal in these patients. This demonstrates that POIS is not associated with disorders that cause an increased IgE. Moreover, POIS also occurs in men without any known allergy.[3,5,8] Waldinger[2] also recently reported the incidence of POIS before and after sterilization in 3 men, suggesting that the antigen triggering the immunologic reaction in POIS is not bound to spermatozoa, but instead is related to the seminal fluid. Interestingly, Waldinger[2] also reported the first case of a woman complaining of POIS symptoms. He postulated that the antigen triggering the POIS symptoms might be produced by prostatic tissue in men or, conceivably, prostatic-type tissue in women, which is localized around the upper wall of the vagina.

In contrast to the autoimmune-allergy hypothesis proposed by Waldinger et al, Jiang et al[6] proposed that IgE-mediated semen

allergy in men might not adequately account for POIS symptomatology. Jiang et al postulated that chemical imbalances in the brain might be the physiologic basis for POIS with psychological conditions serving as risk factors. Using a different grading system and SPT procedure from Waldinger et al, Jiang et al performed SPTs and intracutaneous tests (ICTs) with autologous semen in a patient with POIS and insomnia, anxiety, and mild obsessive-compulsive disorder and 3 healthy volunteers. They also measured serum-specific IgE for semen in the affected patient and in 2 of the healthy volunteers. In the patient with POIS, the SPT reaction was mildly positive at 1:10 dilution and the ICT reaction was positive at 1:100 dilution. In the 3 healthy volunteers, SPT reactions were negative and ICT reactions were positive at titers of 1:10 and 1:100. These results demonstrated that healthy controls can have positive skin reactions to autologous semen, possibly because of inflammatory cytokines and chemokines in the seminal fluid.[6] Seminal fluid-specific IgE, which is detected in women with allergies to semen, was undetectable in the serum of the patient with POIS.[6] Jiang et al[6] concluded that an IgE-mediated mechanism was less likely in POIS. Instead, they compared the symptoms of POIS with opioid withdrawal, which includes similar physical and psychological manifestations. They argued that patients with POIS might have a disorder involving endogenous μ-opioid receptors, because the mechanism of orgasm consumes large quantities of endogenous opioids in such patients, resulting in symptoms similar to opioid withdrawal.[6] An alternate hypothesis proposed by Ashby and Goldmeier[3] in their case report is that POIS is driven by a disordered cytokine or neuroendocrine response. This was supported by the improvement of POIS symptoms in the patient after administration of prophylactic diclofenac, a non-steroidal anti-inflammatory medication.[3]

MANAGEMENT

Because POIS is a rare condition that is likely underdiagnosed and under-reported, there are no recognized treatment modalities for POIS. Patients with POIS-like symptoms have been treated with antihistamines, selective serotonin reuptake inhibitors, and benzodiazepines.[9] Hyposensitization therapy with autologous semen in 2 Dutch men with POIS was successful, with 60% and 90% improvement of POIS complaints at 31 and 15 months, respectively.[8] However, this was not a randomized placebo-controlled clinical trial, so the treatment efficacy remains unconfirmed. Another successful trial of therapy with non-steroidal anti-inflammatory medication (diclofenac) succeeded in alleviating symptoms (up to 80% improvement) and allowed the patient in that case report to increase his sexual frequency from 2 to 4 times a month.[3] However, non-steroidal anti-inflammatory drug therapy failed in other patients, highlighting the need for further investigation into the nature and treatment of POIS.[10] In addition, many alternative therapies have been suggested to be efficacious in improving POIS symptoms, including niacin, olive leaf, fenugreek, saw palmetto, and wobenzym N.[11]

CONCLUSION

POIS is a rare and debilitating condition that causes severe distress in affected men and their partners. It is a chronic disorder that manifests as a constellation of flulike and allergic symptoms that begin seconds, minutes, or hours after ejaculation. The symptoms spontaneously disappear after 3 to 7 days. The prevalence of POIS remains unknown, but there have been an increased number of self-reported cases since Waldinger et al proposed the 5 preliminary criteria. There are 7 clusters of symptoms that are associated with criterion 1. Although presentations of men with POIS can vary in symptoms, intensity, and duration, its manifestation remains relatively constant within an afflicted individual. There also is an association between POIS and lifelong PE. There are 2 types of POIS: primary and secondary. POIS has recently been reported in a woman. The exact pathogenesis of POIS remains unknown, but hypotheses include autoimmune-allergic processes, chemical imbalances in the brain similar to opioid withdrawal, and dysregulation in cytokine and chemokine response.[12] Further research on the reactivity of healthy men to autologous semen with the goal of refuting or validating the autoimmune-allergic hypothesis is warranted. Further studies into the roles of neurotransmitters in POIS also could help explain the processes behind POIS. Future study of self-reported POIS cases on internet forums also could yield valuable data on POIS, because the disorder is rare and most men might be hesitant to see a provider for their symptoms. The psychological consequences of POIS also should be further evaluated to yield a better understanding of the effects of the syndrome. The impact of POIS on the partners of men with POIS is another crucial subject that should be studied. There is still no definitive treatment for POIS, but hyposensitization was successful in 2 patients. Elucidating the causes and pathogenesis of POIS can contribute to developing effective treatments for this debilitating condition.

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