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LETTER TO THE EDITOR

Sexual Function

Novel treatment for post-orgasmic illness syndrome: a case report and literature review

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Dear Editor,

Post-orgasmic illness syndrome (POIS) is a rare disorder affecting men, and is characterized by flu-like symptoms that appear immediately or within hours after ejaculation. In 2002, Waldinger and Schweitzer[1] reported the first two cases of POIS and subsequently proposed five preliminary diagnostic criteria for POIS.[1,2] The symptoms were categorized into seven clusters. To avoid these symptoms, patients with POIS tend to minimize the frequency of ejaculation and avoid sexual activity. Therefore, POIS poses a severe mental and psychosocial burden on patients and negatively affects their quality of life by affecting schedules, dampening romantic prospects, and creating internal struggles to avoid eroticism.[3] Previously, the main treatment strategies were focused on drug and hyposensitization therapies.[4] To date, a standard treatment strategy using these therapies has not been established. Here, we report a case of POIS that was successfully treated with surgery after failed immunosuppressive therapy.

In March 2021, a 42-year-old man came to the Department of Urology (Northern Jiangsu People's Hospital, Yangzhou, China) with the chief complaint of flu-like symptoms and rash following ejaculation for two years. Two years ago, he started experiencing symptoms such as exhaustion, palpitations, difficulty finding words, incoherent speech, concentration difficulty, depressed mood, perspiration, ill with flu, general malaise, headache, burning, red/injected eyes, itchy eyes, runny nose, sneezing, dirty taste in mouth, painful muscles, heaviness in the legs, and rash after ejaculation, occurring via sexual intercourse, masturbation, or nocturnal emissions. The flu-like symptoms occurred 1–2 h after ejaculation, and the rest of the symptoms occurred subsequently. Rash was the final symptom to appear, occurring approximately 12–24 h after ejaculation. All the symptoms peaked within 1–2 days and then spontaneously disappeared. One year ago, the patient developed a rash that was very severe compared to previous instances, extending from the right calf to both calves. He visited several physicians and was finally diagnosed with vasculitis. He was treated with prednisone (Pengyao Pharmaceutical Co., Ltd., Wuxi, China) and mycophenolate mofetil dispersible tablets (Sinopharm Chuankang Pharmaceutical Co., Ltd., Chengdu, China) for up to a year. This treatment provided considerable relief from the rash, while the other symptoms were tolerable with no marked improvement. However, because of their increasingly obvious side effects, the dosage and frequency of these drugs were gradually reduced. Prednisone was gradually reduced from 15 mg to 7.5 mg per day and mycophenolate mofetil dispersible tablets were reduced from 0.5 g three times a day to 0.5 g per day for maintenance therapy. In the last several months, the rash recurred and got worse. Among the other symptoms, headache, in particular, worsened and became intolerable.

The patient underwent high ligation of bilateral varicocele 15 years ago, following which transient acute epididymitis occurred in the left testis. After anti-infection treatment, the patient's condition improved and no further attention was paid to the matter. He had a 10-year-old child and firmly refused the need for reproduction. On physical examination, we found an obvious hydrocele in the left tunica vaginalis and significant enlargement of the left epididymis.

After adequate preoperative communication, the patient accepted our preset surgical protocol and provided informed consent. Besides, the surgical procedure was approved by the Ethics Committee of Northern Jiangsu People's Hospital. Preoperative examination included autoimmune antibody screening, hormone level testing, and a skin patch test, along with routine preoperative checks. Autoimmune antibody tests were negative and all hormone levels were within the normal range. The skin patch test was conducted at an andrology laboratory and the result was negative (data not shown).

At first, we performed bilateral scrotal exploration and found a hydrocele in the tunica vaginalis on the left side. In addition, we noted remarkable thickening of the left epididymis and spermatic cord; therefore, left epididymitis was considered. Furthermore, bilateral seminal tract radiography was performed after bilateral deferens separation at the epididymis level. No obvious spillage of the contrast agent was observed. Meilan (Jumpcan Pharmaceutical, Taizhou, China) was injected into the bilateral deferens, and the outflow of Meilan from the catheter was observed, indicating that the seminal duct was unobstructed. Finally, in addition to turning over the testicular sheath, bilateral epididymectomy and bilateral vasoligation (at the epididymal level) were simultaneously performed. Histological examination of the removed epididymis was performed post-surgery, which revealed epididymitis. The operation was successful and the patient was discharged after 4 days. Prednisone and immunosuppressants were stopped 10 days before surgery and were not continued after surgery. Sexual intercourse began 3 weeks after surgery and gradually increased to two times a week. By the two-month follow-up, the

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patient's symptoms, especially rash and headache, which were the most severe, were relieved.

POIS is a rare and debilitating condition, in which affected men experience a range of symptoms that can last approximately 2–7 days after ejaculation. In 2011, Waldinger *et al.*[2] proposed five preliminary diagnostic criteria for POIS. The presentation of the symptoms of POIS varies considerably and is categorized into seven clusters: general, flu-like, head, eyes, nose, throat, and muscle. In our report, the patient experienced symptoms belonging to all seven clusters. The flu-like symptoms occurred approximately 1–2 h after ejaculation, followed by the others. All symptoms peaked within 1–2 days and then spontaneously disappeared. The patient met four of the five diagnostic criteria for POIS. The duration of the symptoms is the only criterium that was not fulfilled. At the onset of POIS, the symptoms disappeared within a week; however, as the disease progressed, the duration increased to as long as 20 days. Strashny[5] first assessed the validity of the diagnostic criteria suggested by Waldinger *et al.*[2] and suggested that POIS symptoms can last for as long as 21 days. According to the updated diagnostic criteria by Strashny,[5] the patient met all five criteria and was finally diagnosed with POIS.

POIS can be classified into two types: primary and secondary.[2,6] In primary POIS, symptoms appear after the first ejaculations during puberty or adolescence. In secondary POIS, symptoms manifest later in life.[7] The occurrence of the two types of POIS was found to be approximately equivalent in study of 45 Dutch Caucasian males.[2] However, the pathogenesis is not well established.[8,9] At present, two main mechanisms are speculated (**Table 1**). First, Waldinger *et al.*[2] hypothesized that POIS is an autoimmune or allergic disorder. Second, Ashby and Goldmeier[10] hypothesized that POIS is triggered by impairment of the cytokine and neuroendocrine responses. Jiang *et al.*[11] proposed a competing hypothesis that POIS is a disorder of the endogenous μ-opioid receptor system and that the symptoms of POIS resemble those of opioid withdrawal. Furthermore, Pierce *et al.*[12] hypothesized that POIS was associated with sympathetic dysregulation. In our report, in addition to the seven clusters of symptoms, our patient experienced rash after ejaculation, which was treated with prednisone and an immunosuppressant. These results strongly suggest that POIS is, at least partially, caused by an allergic disorder. In recent years, some other studies have suspected that POIS is associated with hypogonadism.[6,13] POIS caused by this condition was successfully treated with the administration of human chorionic gonadotropin[13] or testosterone enanthate.[6] However, in our case, the patient's total testosterone level was 10.4 nmol l^{-1}, luteinizing hormone level was 2.97 mIU ml^{-1}, and follicle-stimulating hormone level was 7.85 mIU ml^{-1}, all of which were within the normal range. Therefore, our case of POIS was different from that associated with hypogonadism.

The therapeutic options for POIS are usually selected according to the hypothesized pathogenesis and main symptoms. Treatment options include drug and hyposensitization therapies. Potentially effective drugs mainly include antihistamines, prednisone, nonsteroidal anti-inflammatory drugs, benzodiazepines, selective serotonin reuptake inhibitors, alpha-blockers, silodosin, nifedipine, and flutamide; however, these may vary based on complaints, patients, case series with small sample sizes, and case reports.[1,10,12,14,15] POIS symptoms have been reported to be relieved with niacin, olive leaves, fenugreek, saw palmetto, Wobenzym N, probiotics, and an anti-inflammatory diet.[16] Drug therapy is currently in the exploratory phase, and there is no standard treatment presently available. Hyposensitization therapy was successfully conducted in two Dutch men, with 90% and 60% improvement in POIS symptoms at 15 months and 31 months, respectively.[16,17] Intralymphatic immunotherapy is a promising new method of allergen-specific immunotherapy, and it was first used to treat a Korean man with POIS.[18] The patient's POIS symptoms and sexual dysfunction were both relieved using intralymphatic immunotherapy.[18] Although these data are promising, they were obtained from case reports. In our case, we hypothesize that POIS is caused by repeated contact of the sperm or epididymal fluid and circulating T-lymphocytes in the seminal tract. Moreover, epididymitis may increase local vascular permeability, which may increase the possibility of blood and semen exposure. Therefore, we believe that epididymectomy and vasoligation are effective ways to eliminate the influence of these two factors. By the 2-month follow-up, the patient's symptoms, especially rash and headache, which were the most severe symptoms, were relieved. The patient was able to ejaculate twice a week by intercourse. To the best of our knowledge, ours is the first study to use surgical processes such as seminal tract radiography, epididymectomy, and vasoligation in the treatment of POIS.

Currently, there is no study assessing the outcomes of POIS treatment over a long period or life-time follow-up period. Although patients respond positively to drugs, it does not indicate that the drug

Table 1: Studies evaluating the purposed mechanism and treatment

Study	*Year*	*Design*	*Cases (n)*	*Purposed mechanism*	*Treatment*
De Amicis *et al.*[8]	2020	CR	1	Psychological disorder	Immunotherapy
Reisman[15]	2021	CS	14	NA[a]	Treatment modalities Highly selective alpha 1A blocker (silodosin) If unresponsive, ibuprofen If still unresponsive, prednisone
Pierce *et al.*[12]	2020	CR	1	Sympathetic dysregulation	Alpha-blockers (terazosin and alfuzosin)
Takeshima *et al.*[6]	2020	CR	1	Hypogonadism	NSAIDs (celecoxib) followed by TRT
Bolanos and Morgentaler[13]	2020	CR	1	Testosterone deficiency	Subcutaneous injections of hCG
Kim *et al.*[18]	2018	CR	1	Allergic type I hypersensitivity reaction	Intralymphatic immunotherapy[b]
Depreux *et al.*[19]	2018	CR	1	Involvement of neurobiochemical mediators	NA
Jiang *et al.*[11]	2015	CR	1	Disorder of the endogenous μ-opioid receptor system	NA
Waldinger *et al.*[2]	2011	CS	45	Combined types I and IV allergic reaction	NA
Waldinger *et al.*[17]	2011	CR	2	Immunogenic/allergic etiology	Hyposensitization treatment
Waldinger and Schweitzer[1]	2002	CR	2	NA	Benzodiazepines and SSRIs[c]

[a]Silodosin, which can cause anejaculation, was an effective treatment in 57% of the POIS patients. [b]Intralymphatic immunotherapy plus prescription drugs, including NSAIDs, antihistamine, and mucolytic drugs. [c]Combined use of flutamide to diminish ejaculation frequency. CR: case report; CS: case series; hCG: human chorionic gonadotropin; NSAIDs: nonsteroidal anti-inflammatory drugs; NA: not applicable; SSRIs: selective serotonin reuptake inhibitor; TRT: testosterone replacement therapy; POIS: postorgasmic illness syndrome

will be effective for a long time. In the present case, prednisone and the immunosuppressant were initially effective, but gradual occurrence of side effects led to a reduction in their dosage and frequency, after which the patient's symptoms recurred and worsened. Medical therapy can only relieve a part of the patient's symptoms. In other words, a single drug may be unable to control all the symptoms, unless etiological treatment is performed. As reported, a remarkable remission of the disease was achieved in patients with POIS associated with hypogonadism by treatment with human chorionic gonadotropin[6] or testosterone enanthate.[13] If POIS is triggered by allergies, it may be treated by isolating the allergens. For patients with risk factors for allergies, it is possible to obtain encouraging results through local exploration of the seminal tract. However, this method may not always yield favorable results, since an orgasm is a complex biochemical event and complete neurophysiological process but not just the physical ejaculation of semen.[12] Furthermore, semen comprises the seminal vesicle fluid and prostate fluid as well as other fluids. Our report provides an insight into an alternative treatment for POIS. We believe that surgical interventions should be conducted in selected patients, after comprehensively considering their reproductive needs, basic diseases, and their own requirements.

In conclusion, for patients with POIS, treatment should be determined according to the hypothesized pathogenesis and main symptoms. For patients with abnormalities detected during specialized physical examination, it is possible to obtain encouraging results through local exploration of the seminal tract. Bilateral epididymectomy and bilateral vasoligation can be used as alternative treatments with promising outcomes. However, as long as surgery is not established as the standard therapy, it should be considered as the last resort and performed only in selected cases. More large-scale randomized controlled trials are needed to confirm the effectiveness and safety of surgical treatments for POIS.

AUTHOR CONTRIBUTIONS

TBH was responsible for data collection, literature review, and manuscript drafting. JJY contributed to data collection, follow-up and helped to revise the manuscript. ZYL and YJD conceived the study, participated in its design and coordination, and helped to revise the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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