Seminal Plasma Hypersensitivity and Successful Intravaginal Graded Challenge

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Citation

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Abstract

Human seminal plasma protein hypersensitivity (SPH) is characterized as an immunologic reaction against glycoprotein antigens in seminal plasma. It can present with post-coital systemic and local symptoms which can be treated with local subcutaneous injections or intravaginal graded challenges (IVGC's). Our goal was to gain a better understanding of SPH and report on the patients who presented with SPH to our clinics. Data were collected on current age, types and onset of symptoms, number of partners with whom symptoms occurred, allergy history and skin testing results. Fifteen patients were evaluated and diagnosed with SPH at our facilities. The majority experienced onset of symptoms in their twenties. Six of fifteen patients (40%) had symptoms with their first exposure to vaginal intercourse. Nine of fifteen patients (60%) experienced local symptoms only and the remaining six patients (40%) had both local and systemic symptoms. Five out of thirteen patients (38.5%) who were skin prick tested had a positive result to fresh semen. Five out of seven patients (71.4%) who underwent IVGC were successful in achieving desensitization.

INTRODUCTION

Human seminal plasma protein hypersensitivity (SPH) was first reported in 1958 by Dutch gynecologist, Dr. Specken.1 Despite increasing reports of SPH, it is often under recognized.3 SPH is characterized by an immunologic reaction against a 34 kDa8 prostate-derived glycoprotein antigen in seminal plasma, which is present in all male semen. The antigen being present in all males makes SPH non-specific to individuals.19 Current research suggests that the allergic reaction is most likely mediated by a classical IgE mechanism, resulting in a local or systemic reaction.2 There have been reports of SPH also associated with Type III and Type IV hypersensitivity reactions and fixed eruptions on the skin.7,14

The immunologic response to SPH typically occurs within 30 minutes post-coitus and presents with localized reactions such as urticaria, vaginal itching, or burning.7 Patients can also present with systemic reactions such as wheezing, shortness of breath and anaphylaxis.10 There have been reports of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and violent pelvic pain, with SPH reactions.13,15 The reason SPH reactions have occurred after the first exposure to semen is still unknown, though hypersensitivity may develop from cross reacting antigens.1 For some, interrupted exposure to semen may play an important role in initiating the allergy as occurs after a pregnancy,3 after a hysterectomy,4 partner's vasectomy17 or partial prostatectomy.18 Additionally, a patient or family history of atopy is often present in those with SPH. However, these have not been identified as significant risk factors and are not sufficient for diagnosis.11

The treatment of choice is complete avoidance, which is attained by abstinence or condom usage. However, these measures may be undesirable for many women, such as those trying to conceive. For those presenting with mild SPH such as local irritation and pruritus, prophylactic anti-histamines20 and non-steroidal anti-inflammatory drugs15 such as mefenamic acid21 have proven successful. As attempts with antihistamines and cromolyn cream have been often unsuccessful with more serious reactions, immunotherapy has been now recognized as an effective treatment. Local subcutaneous injections with fractionated human seminal plasma have been successful in desensitizing women with severe reactions such as anaphylaxis.4 Another largely successful approach is to perform an intravaginal graded challenge (IVGC) using whole seminal plasma, which has been successful at desensitizing patients with local and/or systemic symptoms. IVGC knowledge needs to

be expanded because its mechanisms of actions have only been postulated- limiting its potential to be catered to the individual patient.5 It is recommended to first attempt IVGC before subcutaneous desensitization due to its lower cost, convenience24 and success rate.5

It is estimated that up to 40,000 women in the United States may have SPH.22 Despite these estimates, only about 90 cases of SPH have been reported in previous literature, and most of these reports described only one to three patients at a time. We report here fifteen patients presenting with SPH that have been seen at our institution.

METHODS

IRB approval was obtained from both The New York Presbyterian Hospital and Beth Israel Medical Center. Our patient databases were searched for females with the ICD 9 code of 995.3, allergy unspecified not elsewhere classified. These charts were then searched for a diagnosis of a semen allergy. Of the identified cases, information was collected regarding age of onset, number of partners with whom symptoms occurred, types of symptoms, surgical history, allergy history and skin testing results. Written consent was obtained for each patient prior to testing and IVGC.

RESULTS

Fifteen patients between 1995 and 2011 were evaluated and diagnosed with SPH. Sexually transmitted diseases were excluded prior to diagnostic testing for SPH. With all patients, allergic symptoms appeared within 1 hour after unprotected intercourse and did not occur with the use of a condom.

Table 1 summarizes the patient profiles, including past medical and sexual histories. Of the fifteen patients, the majority experienced the onset of symptoms in their twenties. The age of onset ranged from 18 to 49 years, with an average age of 24 years. While six of the fifteen patients (40%) exhibited symptoms after unprotected intercourse with their first partner, the remaining nine (60%) did not show any symptoms until intercourse with later partners. Furthermore, eight of the women (53.3%) acquired symptoms with only one specific partner. It was noted that all eight of these women were in monogamous, long-term relationships.

Thirteen of fifteen patients (86.7%) had other atopic diseases, most commonly nasal allergies. Other allergic conditions included eczema, food allergies, and asthma (Table 1). Eleven of the fifteen patients (73.3%) had family members with various allergic conditions, including allergic rhinitis and asthma. Only one patient was neither atopic nor had a family history of allergies.

Table 1

Patient Profile

Age of Onset (in years)	*Number of patients*
<20	5
20-29	6
30-39	3
40-49	1
Onset of SPH	
First partner	6
Subsequent partner	9
History of atopy	
Nasal allergies	9
Asthma	6
Eczema	3
Food allergies	1

Thirty three percent (5/15) developed both local and systemic symptoms. Nine patients (60%) presented with only local symptoms isolated to the vaginal area and there were no cases of only a systemic reaction. One patient experienced only a localized rash on the external skin upon contact with semen (Table 2). For all fifteen women, condom use prevented all symptoms.

Table 2

Symptom Profile

Symptomatology	*Number of patients*
Local and Systemic	5
Local only	9
Systemic only	0
Cutaneous	1
Presentation of symptoms	
Local	
Pruitus	14
Burning	14
Swelling	12
Systemic	
Shortness of breath	3
Generalized hives	2
Laryngeal symptoms	1
Hypotension	1
Time of onset of symptoms	
Within 2 min	4
Within 5 min	9
5 min- 1h	2
> 1 h	0

The most common symptoms experienced were itching, burning, and swelling. Two patients (13.3%) also experienced shortness of breath immediately following intercourse. Table 2 summarizes remaining symptoms manifested by patients. Symptoms most commonly appeared within 5 minutes post coitus, though for some, symptoms took only seconds to develop.

Patient histories did not reveal any pregnancies or surgeries that occurred near the onset of SPH, but one patient reported developing initial symptoms around the time of an intrauterine device (IUD) insertion.

Skin prick tests were performed on thirteen women with each of their partner's semen. Two patients refused testing. Results of prick testing with dilutions of 1:1000, 1:100, 1:10 and undiluted semen were recorded. Intradermal testing results with undiluted semen were recorded as well. Five of the thirteen patients (38.4%) had a responsive skin prick test with either diluted or undiluted semen. Two of the five patients with a positive test had a history of a systemic reaction. Seven patients who showed a negative response to the prick tests underwent intradermal testing. All 7 who underwent intradermal testing elicited a positive result to the undiluted semen intradermal test (Table 3). Two male partners tested as controls had positive wheal and flare reactions to intradermal testing but had negative reactions to skin prick testing.

Table 3

Prick and Intradermal Testing (a)

	Type of Reaction[c]	Prick 1:100	Prick 1:10	Prick Undiluted	Intradermal Undiluted	Response to IVGC treatment
Pt 1	Local	0	0	Positive 4 mm wheal 11 mm flare	----	No symptoms upon exposure
Pt 2	Systemic, Local	N/A	N/A	N/A	----	----
Pt 3	Local	0	0	0	Positive 8 mm wheal 15 mm flare	Itching and swelling
Pt 4	Systemic, Local	0	0	Positive 3 mm wheal 10 mm flare	----	----
Pt 5	Local	0	0	Negative 2 mm wheal 6 mm flare	Positive 10 mm wheal 28 mm flare	No symptoms upon exposure
Pt 6	Systemic, Local	N/A	N/A	N/A	----	----
Pt 7	Local	0	0	0	Positive 10 mm wheal 20 mm flare	----
Pt 8	Local	0	0	0	Positive 10 mm wheal 20 mm flare	----
Pt 9	Local	0	0	Positive 6 mm wheal 20 mm flare	----	No symptoms upon exposure
Pt 10	Systemic, Local	Negative 2 mm wheal 8 mm flare	Positive 4 mm wheal 13 mm flare	N/A	----	No symptoms upon exposure
Pt 11	Systemic, Local	0	0	0	Positive 6 mm wheal 15 mm flare	----
Pt 12	Local	0	0	Positive 3 mm wheal 12 mm flare	----	----
Pt 13	Local	0	0	0	Positive 8 mm wheal 20 mm flare	No symptoms upon exposure
Pt 14	Local	0	0	0	Positive 4 mm wheal 11 mm flare	----
Pt 15	Local	0	0	0	----	Itching and swelling

a. *Results are recorded greater than the saline control.*
b. *No participating patients responded to skin pricks with dilutions of 1:10,000 and 1:1,000. Patients 2 and 6 did not perform skin prick testing to those dilutions.*
c. *"Type of Reaction" refers to presentation of symptoms, either local and/or systemic, upon initial clinical examination.*

Of all fifteen patients, seven elected to undergo IVGC following the protocol of Matloff.5 Prior to IVGC, these women avoided unprotected intercourse due to the inability to tolerate symptoms. A fresh whole semen sample was obtained from each patient's partner the morning of the procedure. Serial dilutions of 1:10,000, 1:1000, 1:100, and 1:10 were prepared and 2 mL of increasing strengths of these dilutions were administered every 20 minutes intravaginally. This was followed by administration of 2 mL of undiluted semen. Other than some complaints of mild burning, no significant reactions during the procedure were observed. Patients were instructed to have intercourse every 24-48 hours to maintain the desensitized state. Desensitization through IVGC was successful in five of the seven patients (71.4%). These patients reported having either no or insignificant local symptoms at least 2 weeks post-procedure. Post-procedure, each one was able to have intercourse with either no symptoms or minimal symptoms. Two patients who successfully completed the procedure had localized itching and swelling with unprotected intercourse the night after the procedure.

DISCUSSION

Because SPH is such a rare disorder, it is often under-recognized and improperly diagnosed. 3,25 SPH can be associated with stress and anxiety for these women, often leading to the deterioration of personal relationships.12 Therefore, early detection and subsequent treatment is essential to avoid the discomfort for many patients.

Although factors influencing the onset and course of SPH are still unknown, there have been reported cases of women developing SPH after a temporary cessation of sexual intercourse. For these women, resumption of intercourse results in an allergic reaction to their partner's semen.3 However, none of our patients in this study had a pause in sexual activity preceding the onset of the semen allergy. One patient developed her SPH after insertion of an IUD, which had previously been reported in other women as was published in a series by Shah and Panjabi.7

In addition to seminal protein antigens, it has been noted that exogenous transferred antigens carried in seminal plasma fluid have caused SPH. In one report, a woman allergic to nuts developed a severe systemic reaction after intercourse with her partner who had just eaten walnuts. On examination, the partner's seminal plasma contained detectable amounts of walnut protein.6 A well-publicized case was also documented in a woman with nut allergies who developed anaphylaxis after intercourse with her partner who had just consumed Brazil nuts.23

The atopic profile of patients in this report is similar to that documented in previous reports. Our patient population revealed an 87% prevalence of atopic disorder history, a finding consistent with a previous review by Bernstein et al. (84% of women with SPH also had previous allergies in their study).3 The age of onset and presenting symptoms were also similar to previous reports,3 although the level of skin prick testing sensitivity varied in the literature.5,10,11

Of interest is one patient who had unprotected intercourse with ten partners and developed allergic symptoms to nine of them. It has largely been found that the allergen causing SPH is found in the prostate gland and is not exclusive to individual males.8 This patient's response appears classical for such an antigen. Eight of the fifteen patients experienced symptoms during intercourse with only a single partner. Five of the thirteen patients (38.5%) tested with a skin prick test to semen had positive results. One patient had a negative response to a skin prick test. However, she consented to IVGC therapy and had evidence of contact urticaria upon desensitization. The remaining seven of the thirteen patients (53.8%) had positive intradermal tests. Two male partners tested as controls also had positive intradermal tests, which suggest an irritant reaction to intradermal skin testing.

It is unclear why two patients had a recurrence of symptoms with unprotected intercourse the night after the procedure. Inability to maintain desensitization via IVGC may have been due to the quantity of semen to which patients were exposed, or to a "dilutional effect" from multiple other proteins in seminal plasma and/or an "inhibitory effect" by large molecular weight proteins which prevent T-lymphocyte responses.3

While treatment of SPH has the obvious benefit of relieving symptomatic discomfort as well as life threatening anaphylactic reactions, it has also provided a means for natural conception. There are documented methods of successful natural conception in patients who were not able to do so prior to treatment. Subcutaneous immunotherapy or IVGC have been able to reduce hypersensitivity, thereby allowing natural conception. Success rates in the previous literature have reached as high as 100%, provided patients avoid interruptions in exposure after treatment.3,5 For women who are extremely symptomatic or unable to undergo these procedures, intrauterine insemination with washed spermatozoa and in vitro fertilization have been successful.9 Regardless of treatment method, women with SPH have been able to conceive, showing that SPH is not associated with infertility.

While successful treatments have been recorded previous in case studies, there is currently no literature documenting the effectiveness of this treatment in a larger patient population. Though our success rate of desensitization via IVGC was 71.4%, the number of cases we attempted to desensitize was small.

IVGC improves patient care by avoiding potentially fatal symptoms and improving quality of life. This therapy has been proven to be widely successful given the patient follows through with maintaining the desensitized state by performing intercourse every 24-48 hours.5,15,24

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