

Characterization of patients with suspected seminal plasma hypersensitivity

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ABSTRACT

The epidemiology of seminal plasma hypersensitivity (SPH) is unknown. Case reports and a previous survey have identified two distinct phenotypes: localized and systemic reactors. The objective of this study was to use an Internet-based questionnaire to characterize and examine the differences among a population of women with suspected SPH. A questionnaire designed to distinguish women with probable SPH was made available via the Internet. Systemic symptoms included generalized pruritus, urticaria, angioedema, wheezing, chest tightness, shortness of breath, dizziness, and loss of consciousness whereas localized symptoms included vaginal burning, pain, swelling, erythema, or blister formation. Respondents with localized or systemic symptoms and whose symptoms were prevented with the use of a condom were included in the analysis. Frequency and means were calculated and further analyzed using chi-square and t-test analyses. A total of 165 women with probable SPH, 79 with systemic symptoms and 86 with only localized symptoms, were included in the analysis. Systemic compared with localized respondents were significantly older (mean age, 29.2 years versus 26.4 years; $p = 0.01$), had longer duration of symptoms (mean, 58 months versus 40.8 months; $p = 0.03$), and more frequently reported a family history of atopy (65.8% versus 50%; $p < 0.05$). Interestingly, significantly more systemic compared with localized respondents reported dog sensitization (11.4% versus 2.3%; $p = 0.02$). Localized and systemic SPH are more common than previously realized and should be considered in the differential diagnosis of anaphylaxis, vulvovaginitis, and dyspareunia. Additional research investigating the epidemiology, immunopathogenesis, and treatment of this disorder is warranted.

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Seminal plasma hypersensitivity (SPH) is a spectrum of systemic and/or localized clinical symptoms after exposure to specific protein components in seminal fluid.^{1–3} Systemic SPH symptoms can include diffuse urticaria; facial, tongue, lip, and/or throat angioedema; stridor; wheezing; dyspnea; abdominal, pelvic, and/or vulvovaginal pain and swelling; nausea; vomiting; diarrhea; general malaise; hypotension; loss of consciousness; and complete circulatory failure. Localized SPH symptoms include postcoital vulvovaginal burning, pain, redness, labial swelling, and vesicle formation. Systemic symptoms can occur with or without localized symptoms. Systemic reactions typically occur within 30 minutes postcoitally after exposure to seminal fluid but can be delayed in onset over 2–3 hours and typically resolves over a 24-hour period or sooner after treatment with antihistamines.³ For localized reactions, symptoms typically begin immediately postcoitally and persist for several hours to days.^{2–6}

Currently, the prevalence and incidence of SPH is unknown. Since the first report by a Dutch gynecologist, J.L.H. Specken, in 1958,² numerous cases of SPH have been described in the literature.^{6–9} An extensive literature review of SPH cases describing 32 cases reported between 1958 and 1989⁶ found that symptoms typically began between 20 and 30 years of age in 56% of the cases and 84% of women reported dermatitis, urticaria, and pruritus and 22% reported anaphylaxis. Interestingly, women experiencing symptoms after first-time intercourse was reported in 40% of cases.⁶

Previously, our group analyzed the results of a validated questionnaire completed by 1073 women who suspected they had symptoms consistent with SPH. Of the original 1073 respondents, 130 women were determined to have probable SPH based on their questionnaire responses.⁴ Women were considered “probable” for SPH if they reported two or more symptoms consistent with localized and/or systemic SPH and had complete prevention of symptoms with the use of a condom. Of the 130 women with probable SPH, 46 (35%) reported localized symptoms and 84 (65%) reported systemic symptoms. The mean age of onset was 24 and 23 years, respectively, for localized and systemic reactors. Similar to early reports, onset with first-time intercourse was reported in 43.4% for localized reactors and 20.2% of systemic reactors. This population was not overly promiscuous considering that the average number of sexual partners for localized and

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systemic reactors was 1.7 and 1.4, respectively. A history of atopy was reported in 50.7% of women with probable SPH. Although this retrospective survey did not provide definitive prevalence data on SPH, it was extrapolated from the questionnaire response rate and the number of women with probable SPH that 20,000–40,000 women in the United States could potentially suffer from this condition.⁴

Most recently, the validated questionnaire previously used to identify women with probable SPH has been posted on the Internet. Here, we expand the reporting of patient characteristics as well as examine differences between women with systemic and localized SPH who have completed this questionnaire online over the past 2 years.

METHODS

An electronic version of a questionnaire (Table 1) previously designed to query women suspected of having SPH was made available online.⁷ This questionnaire, although not previously validated using the statistical methods applied for this purpose, has previously been found to be effective for identifying women with probable SPH.² Respondents were not solicited to complete this questionnaire. Questionnaires were collected from December 2008 through January 2011. Only respondents with localized or systemic symptoms whose symptoms were prevented with the use of a condom were included in the analysis. Frequency or means were calculated for each questionnaire response. Respondents who answered in the affirmative to having generalized itching, hives, chest tightness, shortness of breath, cough, wheezing, dizziness, faintness, complete collapse (shock), or unconsciousness were classified as systemic reactors. All other respondents were grouped as localized reactors. Chi-square and *t*-test analyses were used to examine differences between localized and systemic reactors. A value of $p < 0.05$ was considered significant.

RESULTS

A total of 213 questionnaires were submitted of which 165 were included in the final analysis. Forty-eight surveys were excluded from the final analysis because of symptoms that were not prevented with condom use or failure to submit a response. Of the 165 respondents included in the analysis, 79 were characterized as systemic with the remaining 86 were characterized as localized reactors. Baseline characteristics for localized and systemic reactors are described in Table 2. Systemic reactors were significantly older (29.2 years) than localized reactors (26.4 years) at the time of survey. Duration of SPH symptoms at time of survey was significantly longer in systemic compared with localized reactors (58 months versus 40.8 months). No

significant difference was observed between systemic (24.2 years) and localized (22.5 years) reactors in age of onset. Symptoms after first intercourse were reported in 50.6 and 38.4% in systemic and localized reactors, respectively. Systemic respondents (65.8%) reported more frequently a family history of atopy than localized respondents (50%; $p < 0.04$). Of note, 78.5% of systemic reactors and 69.8% of localized reactors experienced symptoms exclusively with their current sexual partner. There were no significant differences between respondent groups reporting recent pregnancy, gynecological surgery, or other gynecological problems or differences between systemic and localized reactions with respect to environmental, food, or drug allergies. Prior allergen skin-prick testing was reported in 30.4 and 27.9% of systemic and localized reactors, respectively. Of those reporting prior allergy testing, systemic reactors were more likely to report dog sensitization compared with localized reactors (11.4% versus 2.3%). Chronic candidiasis was commonly reported by both systemic and localized reactors (43% versus 41.2%) but no significant difference in the number of vulvovaginal candidiasis infections was evident when the two groups were compared.

The clinical symptoms reported by the 79 women classified as systemic reactors are summarized in Table 3. Generalized itching was very prevalent among systemic reactors (93.7%) and urticaria was only reported in 19 of 79 (24.1%) of these women. Respiratory symptoms were prevalent with 15.2% reporting chest tightness and shortness of breath, 6.3% reporting cough, and 7.6% reporting wheeze. Dizziness and faintness were reported by 19 and 13.9% of women with systemic reactions, respectively. More ominous symptoms such as complete vascular collapse and unconsciousness were reported in 2.5 and 1.3% of these women, respectively.

Comparison of localized symptoms for both systemic and localized reactor groups is summarized in Table 4. Severe vaginal burning was the most common localized reaction reported by both groups but was significantly more prevalent among localized reactors. There was no significant difference between groups in the number of other localized symptoms reported.

DISCUSSION

Based on the results of this online survey, SPH appears to be more common than previously recognized considering that 63% of respondents were characterized as having probable SPH. Furthermore, the respondents to this survey could be classified into one of two distinct phenotypes, systemic and localized reactors, which have previously been well described.^{4,10}

Onset with first intercourse in this study was reported in 50.6 and 38.4% of systemic and localized

Table 1 Seminal plasma hypersensitivity questionnaire

1. How long have you had symptoms? A. months B. years

2. Do you have these symptoms exclusively with your current sexual partner? A. Yes B. No

3. If not, how many times have you experienced a reaction with other sexual partners? _____

4. Did you have the reaction on your first intercourse? A. Yes B. No

5. If the answer to the above is no, how many years after your first intercourse did the first reaction occur?
A. _____ months B. _____ years

6. Before the first reaction did you have:
A. A recent pregnancy? A. Yes B. No
B. Recent gynecologic operation? A. Yes B. No
C. Other gynecologic problem? A. Yes B. No

7. How soon after intercourse do your reactions occur? A. _____ Minutes B. _____ Hours
C. _____ Days

8. How long after intercourse do your reactions last? A. _____ Minutes B. _____ Hours
C. _____ Days

9. Do you have the following symptoms?
A. Generalized itching? A. Yes B. No
B. Hives? A. Yes B. No
C. Chest tightness? A. Yes B. No
D. Shortness of breath? A. Yes B. No
E. Cough? A. Yes B. No
F. Wheezing? A. Yes B. No
G. Dizziness? A. Yes B. No
H. Faintness? A. Yes B. No
I. Complete collapse (shock)? A. Yes B. No
J. Unconsciousness? A. Yes B. No

10. If your symptoms are localized only to the vaginal tissue and surrounding areas, do you have symptoms of:
A. Deep pain? A. Yes B. No
B. Burning? A. Yes B. No
C. Redness? A. Yes B. No
D. Rash? A. Yes B. No
E. Blisters? A. Yes B. No

11. Does the use of condoms prevent the reaction: A. Yes B. No

12. How old are you now? _____

13. How old were you when the reaction first began? _____

14. Do you have other types of allergies such as asthma, hay fever, hives, or eczema? A. Yes B. No

15. Have you had allergy testing to determine if you are sensitized to seasonal (pollens) and/or perennial (year round) (*i.e.*, dust mite, cat, dog, mold . . .) allergens? A. Yes B. No

16. If yes to the above, which allergens are you sensitized to? (Please list) _____

17. Do you have allergy to foods? A. Yes B. No

18. If so, which one(s)? _____

19. Do you have allergy to drugs? A. Yes B. No

20. If so, which one(s)? _____

21. Does anyone in your family have a history of hay fever, asthma, eczema, or hives? A. Yes B. No

22. Have you been treated for this condition before? A. Yes B. No

23. If so, what types of treatment have you had? _____

24. Have you had any prior evaluation about the possible allergic aspects of your problem? A. Yes B. No

25. Have you had vaginitis due to Candida? A. Yes B. No

26. What is the name and address of the physician who has been treating you most recently for your problem?
NAME: _____
ADDRESS: _____
PHONE: _____

Table 2 Systemic and localized reactors questionnaire responses

	Systemic (n = 79)	Localized (n = 86)	p Value
Mean age, yr	29.2 (SD = 7.9)	26.4 (SD = 6.5)	0.01
Mean age at onset, yr	24.2 (SD = 6.6)	22.5 (SD = 5.5)	0.08
Duration of symptoms, mo	58 (SD = 59.6)	40.8 (SD = 41.1)	0.03
Exclusively with your current sexual partner	62 (78.5%)	60 (69.8%)	0.20
Mean number of partners you have experienced problem	2.79 (SD = 1.1)	2.46 (SD = 1.1)	0.36
Problem experienced with first intercourse	40 (50.6%)	33 (38.4%)	0.11
Mean number of months after first intercourse that problem occurred	47.7 (SD = 54.3)	30.7 (SD = 41.7)	0.11
Before the first reaction, did you have			
Recent pregnancy	8 (10.1%)	4 (4.7%)	0.18
Recent gynecologic operation	3 (3.8%)	4 (4.7%)	0.79
Other gynecologic problem	14 (17.7%)	7 (8.1%)	0.07
Mean time in minutes after intercourse that reactions occur	94.1 (SD = 378.7)	188.3 (SD = 927.2)	0.41
Mean time in minutes reactions last	2947.2 (SD = 3810.2)	2106.5 (SD = 5723.2)	0.28
Report environmental allergy	46 (58.2%)	36 (41.8%)	0.06
Prior allergy prick test	24 (30.4%)	24 (27.9%)	0.73
Reports dog sensitization	9 (11.4%)	2 (2.3%)	0.02
Number reporting food allergy	30 (38%)	22 (25.9%)	0.10
Number reporting drug allergy	35 (44.3%)	26 (31%)	0.08
Family history of allergy	52 (65.8%)	42 (50%)	0.04
Family history of SPH	3 (3.8%)	5 (6%)	0.51
Prior treatment for SPH	9 (11.4%)	6 (7.1%)	0.34
Number reporting chronic vaginal candidiasis	34 (43%)	35 (41.2%)	0.81
Mean number of candida infections per year	4.86 (SD = 3.97)	4.06 (SD = 3.0)	0.34

SPH = seminal plasma hypersensitivity.

Table 3 Frequency of symptoms reported by women with systemic reactions

Systemic Symptoms	n = 79 (%)
Generalized itching	74 (93.7)
Hives	19 (24.1)
Dizziness	15 (19)
Chest tightness	12 (15.2)
Shortness of breath	12 (15.2)
Faintness	11 (13.9)
Wheezing	6 (7.6)
Cough	5 (6.3)
Unconsciousness	2 (2.5)
Complete collapse (shock)	1 (1.3)

reactors, respectively, confirming previous reports by our group and others that SPH occurs after first intercourse in a large percentage of these women.^{4,6} This suggests either a defect in the innate immune response or sensitization of these women to proteins cross-reacting with seminal fluid proteins. Currently, the most

relevant sensitizing protein reported for women with SPH is believed to be prostate-specific antigen, a 33- to 34-kDa serine protease glycoprotein, although other proteins still to be well characterized may also be involved.^{11,12} Recently, a prostatic kallikrein protein isolated from dog epithelial extract was reported to be >80% structurally homologous to human prostate-specific antigen.¹³ Investigators have postulated that women who experienced SPH after first-time intercourse could have been previously sensitized to dog prostatic kallikrein through previous dog exposure. However, this hypothesis still has to be proven and is still very speculative.^{13,14} In our study, although a significantly greater number of women with systemic reactions reported dog sensitization by skin-prick testing compared with localized reactors, the numbers in both groups were relatively small. In our clinical experience treating women with SPH, dog sensitization has not been commonly observed although actual testing of larger numbers of women to identify cross-reacting dog proteins is required. Additional studies investigating the mechanisms that

Table 4 Frequency of vaginal symptoms reported women with systemic and localized reactions

Localized Vaginal Symptoms	Systemic (n = 79)	Localized (n = 86)	p Value
Severe burning	68 (86.1%)	82 (95.3%)	0.04
Redness	60 (75.9%)	70 (81.4%)	0.39
Deep pain	46 (58.2%)	61 (70.9%)	0.09
Rash	28 (35.4%)	19 (22.1%)	0.58
Blister	14 (17.7%)	7 (8.1%)	0.07

can explain onset of symptoms after first-time intercourse are indicated.

There are several limitations associated with this study that warrant mentioning. First, this was a survey study so recall bias is always an inherent concern that could influence the results. However, many of the characteristics reported from this survey have been previously observed by investigators for other populations, indicating that these questionnaire responses are creditable. Second, because this is a survey, there is no way to confirm whether the women diagnosed with probable SPH actually had the condition. Nonetheless, all women considered for SPH treatment at our institution must have specific questionnaire responses that satisfy our criteria for diagnosis before being selected for evaluation and treatment. Using this questionnaire, we have been 100% successful in correctly identifying women with confirmed systemic and/or localized SPH. Finally, population selection bias is always a consideration in questionnaire studies. Because we were only interested in further defining the clinical characteristics of women with probable SPH, it was preferable that respondents had a high likelihood of having SPH. To ascertain the true prevalence of SPH, this questionnaire would have to be completed by a very large randomly selected population of women across the United States. In our previous attempts to assess SPH prevalence it was observed that women who were not affected with this condition were much less interested in completing the questionnaire.

In summary, this study provides clinical information to the practicing allergist/immunologist about women presenting with signs and symptoms of probable SPH. This information should help facilitate a diagnosis of systemic and/or localized SPH so appropriate therapeutic options can be discussed with the patient more expeditiously. This study highlights the need for fur-

ther research regarding the epidemiology, immunopathogenesis, and treatment of SPH.

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