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Characterization of patients with suspected hypersensitivity to cervico-vaginal fluid.

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Abstract

Background: Allergic reaction to seminal plasma was described decades ago. In USA only tens of thousands women are estimated to be affected. Not only seminal plasma, but also cervico-vaginal fluid contains sex-restricted antigens, yet allergy to cervicovaginal fluid has never been reported in medical literature. We came to a suspicion that because immunologic

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tests required to prove such a diagnosis, allergy to cervicovaginal fluid has never been reported yet it is not uncommon.

Objective: The objective of this study was to use an Internet-based questionnaire to characterize the population of men with suspected hypersensitivity to cervico-vaginal fluid.

Methods: A questionnaire designed to cover localized and systemic symptoms of hypersensitivity reaction was made available via the Internet. Respondents with post-coital adverse reactions were invited to participate. Only respondents who presented with at least two symptoms suggestive to hypersensitivity to seminal plasma or cervicovaginal fluid and were negative for STI and known hypersensitivity reactions such as latex allergy were a subject for further analysis. Board-certified dermatologists were surveyed for seeing bona fide cases of cervicovaginal fluid hypersensitivity.

Results: We have identified 52 cases of suspected hypersensitivity to CVF. Both localized and systemic types of hypersensitivity were identified. A substantial number of dermatologists admitted to witnessing cases of hypersensitivity to CVF

Conclusion: Based on data from affected individuals as well as the opinions of dermatologists worldwide we believe that allergic reaction to cervicovaginal fluid is at least as common as seminal plasma allergy. However, remains unreported due to technical difficulties in diagnosis and dermatologists' disbelief in its actual existence.

Key words:

Seminal plasma hypersensitivity; cervicovaginal fluid; post-coital rash; consort contact dermatitis, genital contact allergy,

Abbreviations:

SP - seminal plasma;
SPH - seminal plasma hypersensitivity
CVF - cervico-vaginal fluid;
CVFH cervico-vaginal fluid hypersensitivity

Introduction

Human seminal plasma protein hypersensitivity (SPH), which was first reported in 1958, is characterized by an immunologic reaction against a prostate-derived glycoprotein antigen in seminal plasma (1-7). The allergic reaction is mediated by a classical IgE mechanism, resulting in localized reactions such as urticaria, vaginal itching, or burning. Patients can also present with systemic reactions such as wheezing, shortness of breath, gastrointestinal symptoms or violent pelvic pain (8). There have been reports of SPH also associated with Type III and Type IV hypersensitivity reactions and fixed eruptions on the skin (9,10). Although only 90 cases have been reported in the literature, the actual prevalence of this disease is likely much higher with estimated 40,000 women affected in the United States only (11). In fact laboratory tests for SPH are technically challenging and SPH may be misdiagnosed with vaginitis. Patients' embarrassment and physicians' poor knowledge of this subject also contribute to the underestimation of SPH prevalence.

Not only seminal plasma, but also cervico-vaginal fluid (CVF) contains sex-restricted antigens. CVF, predominantly synthesized by the endocervix, is a complex biological fluid consisting of a multitude of proteins and proteolytic enzymes. CVF also contains secretions from vaginal cells, which include mucins, defensins, complement factors, immunoglobulins,

lactoferrin, and collectins. CVF lubricates the female reproductive tract and during sexual arousal also secretions from Bartholin's glands contribute to the vaginal lubrication. Proteome studies showed that CVF alone contains 77 unique proteins (12). Counterintuitive, not a single case of hypersensitivity to human CVF has ever been reported.

Although one of the authors (MJ) witnessed a bona fide case of hypersensitivity to CVF (CVFH), technical obstacles with acquisition and testing of CVF prevented confirmation of such a diagnosis with immunologic methods. We came to a suspicion that diagnostic challenges and both doctors and patients' ignorance in this matter contribute to the fact that hypersensitivity to CVF has never been reported. However, it may not be uncommon. To test this hypothesis we have created a Internet-based questionnaire directed towards patients experiencing post-coital adverse reactions. We have also surveyed dermatologists worldwide if plausible CFVH cases have been witnessed by other dermatologists. Based on results of the surveys we believe that allergic reaction to CVF is at least as common as SPH. However, it remains unreported due to technical difficulties in diagnostics.

Material and Methods

Survey of anecdotal reports

We have searched Google search engine with common-language key words 'vaginal fluid allergy', 'intimate fluid allergy', 'sex allergy', 'allergy to vagina', and 'allergic to vagina'. We identified symptoms reported by patients in each of the first 20 search engine hits. Testimonials containing any symptoms or laboratory test results suggesting non-allergic aetiology were excluded.

Patient Survey

A questionnaire designed to characterize respondents with probable SPH and CVFH was made available online (<https://www.surveymonkey.com/r/sex-allergy>). Questions were based on available literature in seminal plasma hypersensitivity (8,11,13,14) and post-orgasmic illness syndrome (15,16), the results of anecdotal reports search and symptoms witnessed in author's patients. Surveyed symptoms included burning sensation, pruritus, erythema, urticaria, edema, vesicular or pustular rash, fever or chills, flu-like symptoms, dyspnea, hoarseness, gastrointestinal upset, diarrhea, nausea or vomiting, extreme weakness or hypotension, increased perspiration, difficulty in concentrating, incoherent speech or irritability, extreme weakness or hypotension, and ear pain or ringing sensation. Respondents were requested to specify, among others, if symptoms were local or generalized, and if they appeared after cutaneous, vaginal, oral, or anal contact with seminal plasma or CVF. The questionnaire had English, French, Italian, and Polish language versions and altogether consisted of 830 questions therefore a skip-logic algorithm that selected displayed questions based on language choice, patients' sex, sexual orientation and reported symptoms was implemented. Participants with adverse reactions to SP of CVF were actively recruited in US, UK, Netherlands, France, Italy and Poland through a Facebook invitation targeted at males and females aged 18-65.

Survey of Dermatologists' opinions

Dermatologists, members of the European Academy of Dermatology and Venereology have been invited to participate in the Internet-based survey through the e-mail invitation. The invitation was received by 1890 dermatologists in 51 places all over the world. The survey consisted of 2 questions. In the first question we asked if, in your opinion, were there any allergic reactions to semen or cervicovaginal fluid a substantial medical problem, despite anecdotal reports and wide media coverage and the lack of scientific data on incidence of allergic reactions to seminal plasma and cervicovaginal fluid. The second question was prepared for respondents who have seen personally patients we are interested in. The first question gave the respondents 5 possible answers:

a) 'Yes, true allergic reactions to seminal plasma and cervicovaginal fluid are a common problem. I've seen such cases personally' b) 'Yes, true allergic reactions to seminal plasma and cervicovaginal fluid exist, but are extremely rare. I've seen such cases personally' c) 'Yes, true allergic reactions to seminal plasma and cervicovaginal fluid exist, but I've never seen such a case personally' d) 'Allergic reactions to seminal plasma and cervicovaginal fluid do occur but only due to extrinsic allergens, for example, derived from drugs taken orally, spermicidal agents, lubricants, intimate hygiene cosmetics etc.' e) 'True allergic reactions to seminal plasma and cervicovaginal fluid do not exist. Erythema, pruritus, burning sensation or edema subsequent to mucosal or cutaneous contact with seminal plasma and cervicovaginal fluid are related to epithelial microinjuries and irritating properties of enzymes present in seminal plasma and cervicovaginal fluid.' Like it was mentioned before only respondents who claimed to have seen patients with either SPH or CVFH personally were asked the second question on prevalence of such cases in their practice.

Results

The patient-oriented survey was sent to 19352 persons, out of which 308 completed the survey. Respondents currently on medication or having sexual contacts with patients using some kind of drugs as well as respondents who reported being diagnosed with STI, fixed drug eruptions, allergy to latex, spermicidal or lubricating agents have been excluded from further analysis. Out of remaining 105 respondents, 70 complained of adverse reactions to CVF and 35 reported adverse reactions to SP. Respondents were considered “possible” for CVF hypersensitivity if they reported two or more symptoms consistent with localized or systemic hypersensitivity, a criterion used by Bernstein et al to estimate prevalence of SPH (13). Of 70 respondents with adverse reaction to CVF only 52 fulfilled this criterion and were included in analysis. Based on number of invited individuals the prevalence of CVFH would be estimated to be 0.3% of adult population (18-65 y.o.). With more stringent criterion of at least 3 symptoms consistent with hypersensitivity reaction, the estimated prevalence would drop to 0.1%

Respondents demographics

Among respondents reporting adverse symptoms in contact with CVF dominated young adults aged 20-29 (38%), who would have on average 4.6 sexual partners in a lifetime. Majority (70%) would have sex two times a week or less. Only 30% of respondents ever sought medical consultation of their problem. Among respondents reporting adverse symptoms in contact with SP young adults aged 20-29 were also a dominant group (40%). The respondents would have on average 3,8 sexual partners in a lifetime. Majority (68%) would have sex two times a week or less.

Symptomatology

Erythema, pruritus or burning sensation also edema or whealing in reaction to contact with CVF have been reported respectively in 90%, 77% and 69% of cases. Vesicular or pustular rash was reported only in 33% of cases.

Based on Manhattan distance hierarchical clusterization method, patients could be classified into 2 separate groups – 83% reported local cutaneous reaction while 17% would have a systemic reaction to CVF. Majority of patients reported lesions of early onset with 47% developing lesions within 1 hour, further 24% developing lesions within 6 hours post coitus. More than a half of patients (57%) would develop adverse reactions to CVF with first sexual contact with respective partner. Out of 37% who would develop adverse reaction after more than a month of sexual relation nearly half would do so after a prolonged sexual abstinence. During the course of sexual relation symptoms would gradually subside in 31%, recur with

stable intensity in 42% or aggravate in 27% of cases.

Erythema, pruritus or burning sensation and edema or whealing in reaction to contact with SP have been reported respectively in 95%, 82% and 77% of cases. Vesicular or pustular rash was reported only in 23% of cases. As far as the anatomic location of lesions was concerned only half of patients who reported the feeling of burning sensation or pruritus in the vagina after the contact with SP would report having such a reaction after contact of SP with the skin. Cutaneous reaction was unlikely to occur in patients without mucosal reaction. To the contrary, twice as many respondents reported vesicular lesions on the skin than on the mucosa.

Patients could be clustered into 2 separate groups – 65% reported local mucosal or mucocutaneous reaction while 34% would have a systemic reaction to SP. Majority of patients reported lesions of immediate onset with 56% developing lesions within 1 hour, further 13% developing lesions within 6 hours post coitus. 47% of respondents would develop adverse reactions to SP with first sexual contact with respective partner. Out of 18% who would develop adverse reaction after more than a month of sexual relation nearly two thirds would do so after a prolonged sexual abstinence. During the course of sexual relation symptoms would gradually subside in 18%, recur with stable intensity in 45% or aggravate in 36% of cases.

Survey of Dermatologists' opinions

Of 1890 invited dermatologists, 190 dermatologists from 50 countries took part in the survey. The idea of existence of any true allergic reactions to SP and CVF was rejected 15.3% of dermatologists, further 21.6% believed that allergic reactions may occur, but only due to extrinsic allergens diluted in seminal plasma or CVF such as drugs, spermicidal agents, or lubricants. Of 63% of surveyed dermatologists, who considered hypersensitivity reactions to seminal plasma and CVF as actually existing conditions, one third (n=42) claimed to have witnessed such patients themselves. Out of 42 respondents, 88% reported witnessing cases of seminal plasma hypersensitivity of immediate type and 54.7% would see a patient with delayed type reaction. An immediate-type and delayed-type allergic reaction to CVF has been witnessed by 43% and 38% of dermatologists respectively. Fig 2

Discussion

A population study based on Internet-distributed questionnaire survey has obvious limitations. Because of lack of direct examination by a physician, population of respondents with presumed CVFA could include individuals with other allergic reactions relevant to sexual life such as latex allergy or allergy to medication transferred in bodily fluids. To avoid this, the survey included questions about respondents' or their partners medications and known drug reactions, history of STI, allergy to latex or lubricants were included and all respondents who answered positively to those questions were excluded from further analysis. Although we intended to characterize a population of patients with suspected CVFH, our questionnaire contained questions about hypersensitivity to seminal plasma. By doing so we were able to evaluate our methodology. In fact demographics, reported symptoms, timing of the their occurrence and the course of the condition in our respondents with adverse reactions to seminal plasma are consistent with those reported in the literature in dermatologist-verified cases of SPH. This validates the assumption that our methodology is effective in negative selection of SPH mimics. In line with this we assume that our methodology would be equally valid in negative selection of CVFH mimics. By comparing numbers of invited respondents and numbers of suspected SPH and CVFH cases we estimate the prevalence of CVFH to be at least as common as SPH with up to 0.1% of adult population affected. The relative number of

respondents with suspected CVFH is 1.4 that of SPH group. This may be biased by the fact that patients with SPH could have been provided with more adequate medical information on their condition and hence less likely to participate in our survey. The results of dermatologists' survey support the hypothesis that CVFH is not uncommon with relative number of dermatologists-reported CVFH cases being half of SPH cases. Two thirds of surveyed dermatologists believe in and one fifth have witnessed CVFH cases. This is particularly interesting since hypersensitivity to CVF has been ever described in medical literature.

The emerging image of assumed CVFH is the occurrence of erythematous, macular or urticarial pruritic lesions within minutes to hours post exposure to CVF. Affected person is likely to be in their 20's. Condition may arise both very early and late in the course of sexual relation, yet in the latter case a prolonged sexual abstinence preceding the occurrence of lesion would be expected. Two clusters of affected individuals could be distinguished. Majority suffer from localized cutaneous symptoms, only minority would have a generalized reaction. Our questionnaire included also questions about symptoms occurring in rare cases of type III SPH (10,17). Two of the respondents reported experiencing chills, increased perspiration, gastrointestinal upset, and nausea what could suggest that type III hypersensitivity to CVF may occur in rare cases. Symptoms are likely to be relieved by antihistaminics but not by condom usage as condoms protect the shaft of the penis but are not an effective protection against contact of the groins and scrotum with the vaginal lubricant. Spontaneous gradual improvement over time is common, corresponding with gradual improvement previously reported in cases of SPH (18).

Calioguri et al. (19) proposed that localized form of SPH is a mucosal variant of protein contact dermatitis. Bernstein and Gosh (20) argued that in 50% of cases localized SPH symptoms occurrence after first contact with seminal fluid and vesicular lesions is uncommon, while PCD is characterized by vesicular lesions and requires recurrent exposure to a causative protein. Results of our study are in line with Bernsteins findings and further speak against SPH being a form of PCD. We would assume that also CVFH is not linked to PCD. CVF contains 77 unique proteins to which male immune system wouldn't had been exposed during development what prevents negative selection of reactive T-cell repertoire. It is tempting to attribute CVFH to one of those sex-specific protein, yet another speculative explanation of this phenomenon is also plausible. Kalikreins constitute a substantial part of CVF proteome (21). Kalikreins, including KLK7, are serine proteases involved in the proteolysis of extracellular corneodesmosome components. Elevated activity of kalikreins in the stratum corneum is associated with impaired barrier function and irritation in atopic dermatitis. (22). CVF-derived kalikreins could hypothetically activate the protease-activated receptor 2 (PAR2), resulting in thymic stromal lymphopoietin (TSLP) secretion and a cutaneous T-helper 2 allergic response in the affected individuals.

Gallup and Reynolds (23) proposed that SPH may be an evolutionary mechanism of mate choice. It could function to eliminate mating people without genetic compatibility. The inability to conceive could be a consequence of unpleasant intercourse and minimized frequency of mating as a result of that. Since symptoms of CVFH appear mostly very early in the course of sexual contacts, CVFH could be an additional mechanism contributing to this phenomenon.

The results of this study show that a substantial number of individuals experience symptoms are consistent with hypersensitivity after cutaneous contact with CVF. Further research is required to validate CVFH as a nosological entity. Ideally an IgE immunoblotting of proband's serum and partner's CVF with respective controls would be envisaged. However, in patients with positive prick tests for SP, serum IgE against SP is not always present (24), and this should also be anticipated for CVFH patients. One of the authors (MJ) attempted to achieve this but his patient failed to collect CVF sample. Since the potential antigen is

unknown all secretions contributing to the vaginal lubrication, including Bartholin's and Skene's glands secretion, would also need to be immunoblotted adding to the technical difficulty of such a test. The results of our study also point to the need of increasing awareness of allergic reactions to bodily fluids among both professionals and patients. Nearly 70% of affected individuals have not sought medical consultation. Moreover, nearly 60 years have passed since scientific description of SPH and almost 37% of dermatologists are not aware of its existence. The lack of inclusion of allergy to intimate fluids into differential diagnosis by dermatologists and gradual subsidence of symptoms in a proportion of patients may contribute to the underestimation of the number of affected persons.

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Survey of cases witnessed by other dermatologists

