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Vulvar Vestibulitis as a Neuro-inflammatory Condition: a proposed model and potential treatment options

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Editorial Comment: **Because Dr. Foster's research and conclusion are so exciting, we wanted to print it in its entirety (even though a 2 part series will be required). Please save this volume of Vision and reread it with our soon to be published next issue).**

Part 1

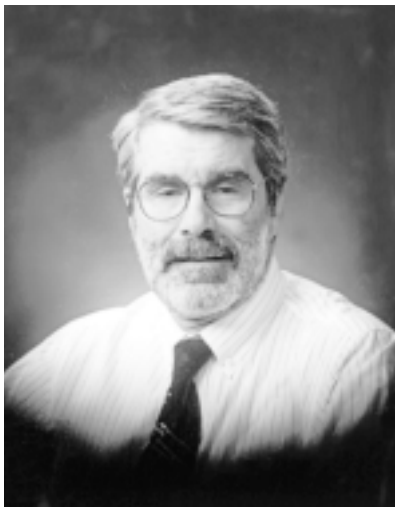
Women with vulvar vestibulitis syndrome (VVS) commonly report long-standing insertional dyspareunia or pain with insertion of a tampon. Classified as a major sub-type of vulvodynia, VVS originates from a myriad of inflammatory insults to the female genital tract. In the susceptible individual, a highly localized region of the lower genital tract develops a syndrome of chronic burning pain, lowered pain thresholds (hyperalgesia) and pain to light touch (mechanical allodynia). VVS commonly presents with dyspareunia, which can be psychosexually devastating. The end result of this condition has included infertility, physical abuse, depression, divorce and suicide. This brief overview suggests that the etiology of VVS may be neuro-inflammatory and that potential treatments directed against pro-inflammatory cytokines may be forthcoming.

Diagnosis of VVS

In terms of diagnosis, VVS is characterized by dyspareunia, focal pain to light touch of the vulvar vestibule, and no identifiable source of pain such as herpes, candida or pemphigoid. Peckham et. al.[1] described the condition as "focal vulvitis" and noted that vestibular inflammation was "rarely seen with the naked eye," whereas vestibular hypersensitivity and allodynia on physical exam were "essential" diagnostic criteria. Exquisite sensitivity to touch was found to be characteristically focal, reproduced with remarkable precision by independent observers, and separated from non-tender areas of the vulva and vagina by a matter of millimeters. In 81% of patients, all painful foci were located on the mucosa of the lower half of the vestibule, between 3:00 and 9:00 inclusive, limited by the line of keratinization (Hart's Line) and the hymeneal ring. The remaining 19% presented with focal areas of tenderness within defined limits of the vestibule but extending toward the urethral orifice. In contrast to other types of vulvodynia, the highly localized findings of pain in vulvar vestibulitis facilitate the development of a clear definition of disease.

Friedrich's criteria[2] remain the standard for diagnosis and include: 1) severe pain on vestibular touch or attempted vaginal entry, 2) tenderness localized within the vestibule, and 3) physical findings of erythema of various degrees. Recognizing a need for an updated classification of all vulvar pain conditions, the 1999 World Congress of the International Society for the Study of Vulvovaginal Disease (ISSVD) convened a group to develop a consensus for a new classification. The group's effort focused particularly on the ill-defined category of chronic vulvar pain without visible dermatosis identified as "Vulvar Dysesthesia (vulvodynia)". They proposed two major subtypes of vulvar dysesthesiae: "generalized" and "localized" vulvar dysesthesia. "Localized vulvar dysesthesia" was synonymous with "vulvar vestibulitis syndrome" and

The President's Perspective



John C. Slocumb, M.D., FACOG • President

The reported association of chronic pelvic pain with sexual abuse, particularly during childhood, has always been a puzzle to me. While in a simplistic sense one might agree that sexual abuse can result in the same anatomic tissues developing chronic pain, however the psychologic and neurologic mechanisms remain unclear. Recent studies have supported the association Collett reported in 1998 that women with chronic pelvic pain (CPP) have a higher lifetime prevalence of sexual abuse. Lampe in 2000 found that sexual victimization before age 15 was associated with CPP and Bodden Heidrich reported in 1999 that sexual abuse was found to be a predictor of the CPP syndrome. Jameson, on the other hand, showed in 1997 that a history of childhood sexual abuse was not a predictor of CPP while women abused both during childhood and as adults was. Rapkin in 1990 reported that while there was an association of both childhood and adult sexual abuse with CPP and with other pain syndromes, there was a much greater association of CPP with physical abuse, both during childhood and as adults. While all of these studies were retrospective, the preponderance of reports have consistently supported the association between abuse and chronic pain.

Now comes the first prospective study by Raphael, et al, Pain 92: 283, 2001, which reports that no significant increase in unexplained pain symptoms were found when childhood victims of sexual and physical abuse, and neglect were compared to controls after a 15-20 year follow-up. Of interest, was the finding that young adults abused in childhood were more likely to remember that abuse if they had unexplained pain, than those with abuse history who didn't have pain. While I believe that unresolved fears, anxiety, PTSD and ongoing life stresses can potentiate pain symptoms and complicate management outcomes, I hope that the simplistic deduction that if a patient has chronic pelvic pain she must have been abused as a child and doesn't remember it will be recognized as another form of medical abuse. Sex may make the world go around, but it cannot explain the enigma of chronic pelvic pain. Because we don't see an obvious cause doesn't mean that it has a psychosomatic origin. I have always felt that if I can reproduce the pain on neurologic exam, the origin is either peripheral sensitization or central (spinal) neuropathic sensitization. There are two kinds of physicians who care for women with CPP-those who don't know the cause of pelvic pain and those who don't know they don't know the cause of pelvic pain. Let us continue to listen to our patients.

Sincerely,

John C. Slocumb, M.D., FACOG
President, International Pelvic Pain Society

...continued from page 1

included vestibulodynia and clitorodynia. Unfortunately, the ISSVD proposal remains unpublished at the writing of this paper and the nomenclature remains controversial.

A search for etiology through case-control studies

Although published case-control studies of VVS[3,4,5] lack a single common risk factor, vulvar inflammation or trauma may serve as a common denominator. Inflammation or trauma may arise from a myriad of events including: recurrent candidiasis, treatment for human papillomavirus (HPV), or trauma during adolescent sexual experience. Two case-control studies[3,4] reported an association between VVS and recurrent candidiasis but also found a common absence of confirmatory wet-mount or cultures for fungus. Based upon full or partial relief of itching and burning with anti-fungal therapy in these cases, candidiasis commonly became the presumed diagnosis. Anti-fungals, such as ketoconazole, have intrinsic anti-inflammatory properties and therefore relief of itching or burning symptoms may not prove a fungal causation.[6] With respect an HPV basis for VVS, HPV-associated DNA has not been found to be more frequent in VVS cases. However, treatments for "presumptive HPV" including application of tricholoacetic acid, podopophyllin, and laser ablation remain suspect as sources of genital injury. A 1 year review (1999-2000) of 246 new visits to the University of Rochester Vulvar Service found that 78% (50/64) of newly referred VVS cases were able to identify a traumatic or inflammatory occurrence in close temporal relationship with the onset of chronic vulvar pain. Traumatic or inflammatory events reported by VVS cases, in order of decreasing frequency, included: recurrent "yeast" (27%), an episode of unusually painful intercourse (13%), delivery of a child (13%), and laser therapy (8%). The odds of a traumatic or inflammatory event preceding VVS was 4.14 (2.76 - 7.89; 95% c.i.) compared to traumatic or inflammatory events preceding other vulvar diagnoses (DC Foster, unpublished). The highest strength of association in case-control study from our clinic, was found between VVS and the Caucasian race (OR=15.73).[4] The basis of this racial difference remains obscure.

Cytokine and neurokine studies of peripheral tissue

Particularly over the last decade, the advent of animal models for neuro-inflammatory and neuropathic pain have advanced the understanding of pain mechanism and potential treatments. For example, rat paw cutaneous hyperalgesia and allodynia can be induced by peripheral injection of pro-inflammatory cytokines: IL-1β or TNF-α. Following local injection of IL-1 β neural discharge from cutaneous sensory fibers to thermal stimuli, within a defined receptive field, increases over 4-fold and the threshold for mechanical sensitivity decreases (becomes more sensitive) by 50 to 60%.[7] Similar to IL-1β, the local injection of TNF-α produces thermal hyperalgesia,[8] mechanical allodynia,[9] increases spontaneous activity of A δ and C fibers,[10] promotes neural demyelination by attacking the oligodendrocyte. [11-13] and promotes reflex sympathetic dystrophy of the hand.[14]

In VVS cases and asymptomatic controls, Inflammatory cytokines: IL-1 β and TNF-α, have been compared from selected regions of the vulva, vestibule, and vagina.[15] Median tissue levels of IL-1 β and TNF-α were 2.3-fold and 1.8-fold elevated, respectively, in women with VVS compared to pain-free women. Regional elevation in inflammatory cytokines in VVS varied with clinical history into two distinct patterns: "hymeneal predominant" and "external vulvar predominant". "Hymeneal predominant" IL-1 β and TNF-α occurred in cases reporting dyspareunia beginning with the first sexual experience or with a new sexual partner. "External vulvar predominant" IL-1 β and TNF-α occurred in women with a history of inflammatory or post-traumatic vulvar skin conditions. Cytokine elevations correlated poorly with inflammatory cell infiltrate and suggested cytokine production from another cell source.

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