National Vulvodynia Association

NVA News

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Vulvodynia in Menopause

By Miranda Farage, Ph.D., et. al.

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The age-related morphological (structural features) and physiological changes of the vulva and vagina over a lifetime are well-established, as is the hormonal mediation of these events. At birth, the vulva and vagina exhibit the effects of residual maternal estrogens which dissipate by the fourth postnatal week. During puberty, adrenal and gonadal steroid hormones induce maturation of these tissues, which continue to undergo changes during the reproductive years linked to the menstrual cycle and pregnancy. At menopause, there is a dramatic loss of estrogen, which leads to vulvar and vaginal atrophy. Pubic hair becomes sparse, the labia majora loses subcutaneous fat, and the skin of the vulva thins. The vaginal mucosa loses glycogen, with a subsequent rise in the vaginal pH and decrease of vaginal secretions. Decreased vaginal blood flow and pelvic floor muscle tone also occur. Symptoms are variable among women, but may include dyspareunia, irritation, burning or itching. As such, the symptoms of vulvovaginal atrophy (VVA) may mimic those of vulvodynia.

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Biomarker Research Offers Hope for Vulvodynia

By Andrea Nackley, Ph.D.

Dr. Nackley is an associate professor in the department of anesthesiology's Center for Translational Pain Medicine at Duke University. Her main research interest has been identifying factors that put some individuals at risk for developing chronic pain conditions.

From an evolutionary perspective, pain is important for our survival. Acute pain occurs in response to environmental stimuli and warns us of potential or actual tissue damage. In the event of actual tissue damage, pain serves to promote wound healing and repair. In some cases, however, the pain outlasts the stimulus and becomes chronic.

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MENOPAUSE

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The transition period to menopause, perimenopause, usually begins at the median age of 45 years and lasts for about four years. Perimenopause is characterized by menstrual cycle irregularity, with an increase in the number of anovulatory cycles (no ovulation). The symptoms vary and include cramps, bloating, and breast tenderness as well as hot flashes, migraine, and vaginal dryness. Menopause is established one year after the last menstrual period.

Estrogens also affect many levels of the pain pathway, including the tissue inflammatory response, sensory neurons and dorsal root ganglia, spinal cord, limbic circuits for affective states, and stress responses. Estrogen receptors present in the central and peripheral nervous systems are known to influence all aspects of neural activity from membrane permeability to gene regulation. The transition into menopause, with the accompanying change in systemic estrogen concentration, therefore, may affect chronic pain.

Diagnosis

The evaluation of postmenopausal women with vulvar pain includes a detailed history and a targeted physical exam. Vulvodynia should always be considered in the differential diagnosis. The history should document the nature of the pain, onset, severity, and effect on everyday life and sexual function. In addition to dyspareunia and pain provoked by any local contact, women with provoked vulvodynia may report constant or intermittent spontaneous discomfort such as burning, aching, rawness, or irritation. Vaginal symptoms, including discharge and bleeding, should be investigated. Nongenital menopausal symptoms, all medications, and all vulvar contacts (soaps, detergents, over-the-counter products) should be reviewed. Recent research has shown increasing evidence for comorbidity of vulvodynia and other chronic pain conditions such as fibromyalgia, interstitial cystitis, temporomandibular joint and muscle disorder, and irritable bowel syndrome. As such, patients with vulvar pain should be asked about symptoms related to these pain disorders as their presence may heighten the concern for vulvodynia.

A careful inspection of the vulva and vagina should be undertaken to rule out an inflammatory, infectious, or neoplastic (abnormal growth) cause of the pain and to support the diagnosis of provoked vulvodynia with the cotton swab test. For instance, the pain of provoked vestibulodynia is elicited by lightly touching the vestibule with a moistened cotton swab. The presence of vulvar lesions does not exclude the diagnosis of vulvodynia. For example, the presence of psoriasis on one labium majus cannot be held responsible for a spontaneous, diffuse, and burning chronic vulvar pain or for introital dyspareunia. Indeed, vulvodynia may

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NVA News

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The National Vulvodynia Association is a nonprofit organization that strives to improve women's quality of life through education, research funding, support and advocacy.

The NVA is not a medical authority and strongly recommends that you consult your own health care provider regarding any course of treatment or medication.

be associated with other non-relevant conditions. In addition, anatomic variants such as vestibular papillae (small bumps) or vestibular erythema (redness) should not be misinterpreted as causes of vulvar pain. As opposed to abnormal vestibular erythemas, physiological vestibular erythemas are not raised, focal (posterior part of the vestibule, particularly around the openings of the Bartholin's gland), symmetrical, and have ill-defined borders.

Pelvic exams should include palpation of the levator muscles to assess for muscle spasm and the bladder and urethra for tenderness. A bimanual exam should be performed to exclude pelvic pathology. Neurologic exam should include searches for (i) sphincter disturbances (urinary, anal) by history-taking, and (ii) objective neurologic abnormalities, including anesthesia, hypoesthesia (numbness) or perineal reflex abolition, i.e., the "anal wink." To conduct this evaluation, the perianal area is scratched gently with the sharp end of a cotton swab and the contracture of the external anal sphincter is observed.

In the absence of any visible vulvar lesions or skin changes, a biopsy is not indicated and will not aid in the diagnosis of vulvodynia. In a menopausal woman, vulvovaginal atrophy is one of the possible causes of provoked vulvar pain, and signs such as loss of pubic hair, labial flattening or fusion, or an elevated pH should be documented. In VVA, a vaginal wet prep shows an increase in vaginal parabasal cells and white blood cells without evidence of any pathogens such as yeast or bacterial vaginosis. Addition of a drop of Wright's stain to the wet prep will more clearly define the presence of parabasal cells. Vaginal cultures should be sent if evidence of infection is present. Vaginal specimens should be systematically taken to look for infection either responsible for or associated with the pain.

A trial of topical estrogen (in the absence of contraindications) should be the first line treatment for menopausal women complaining of dyspareunia, especially if there is evidence of VVA on exam. If symptoms do not resolve with these measures, treatments for vulvodynia should be initiated. Spontaneous diffuse vulvar burning is not a manifestation of VVA and, in the absence of relevant findings, is more likely related to vulvodynia.

Treatment

There is no "one size fits all" treatment for vulvodynia. Experts agree that multifaceted treatment is the best approach to this condition. Choices will depend on the patient, her partner, the local health-care system, and the costs. Vulvar care measures, pharmacological treatments (both topical and oral); physical therapy; and personal, couple, or sexual counseling are all possible components of successful treatment. The National Vulvodynia Association (NVA) is an excellent source of educational materials and actively provides support for these patients (www.nva.org).

Vulvar Care Measures

Gentle genital hygiene is important to prevent irritation that may aggravate vulvodynia. The vulva should be washed with plain warm water only or with a gentle, unscented soap and then patted dry. Vulvar irritants such as bath salts or over-the-counter feminine hygiene products, such as douches, sprays, and scented wipes, should be avoided. Ice packs (easily made by freezing water in a 16 oz. plastic soda or water bottle) can be applied through clothing for temporary relief. Adequate lubrication during intercourse and vaginal moisturizers for noncoital lubrication should be encouraged.

Topical Medications

Lidocaine anesthetic ointment can be used both for symptomatic relief and to reduce coital pain in women with vestibulodynia. External application of lidocaine

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gel 5% 10–20 minutes prior to intercourse aids in reducing pain with penetration with minimal effect on overall sexual sensation in many women. Direct application to the clitoris should be avoided. One study showed that daily application of topical lidocaine was equally effective as biofeedback in relieving symptoms at 12 months, whereas, in another double-blind, placebo-controlled study, lidocaine failed to improve vulvodynia symptoms more than placebo when applied four times a day for 12 weeks. Many topical medications have been used anecdotally or shown to be effective in small studies or case series. These include 2-6% gabapentin formulation, compounded topical estradiol 0.03% with testosterone 0.1%, capsaicin, amitriptyline 2% cream (sometimes combined with baclofen 2%), or nifedipine cream. None of these treatments are evidence-based, and all of them are off-label for the treatment of vulvodynia.

Intolerance to topical treatments is common. Although contact dermatitis has been documented, discomfort (mostly burning) following topical applications is related neither to an allergy nor to an irritation. Diluting topical preparations with tolerated substances, such as lubricating gels, estrogen creams, and mineral or vegetable oils, may be helpful.

Oral Medications

Oral medications for vulvodynia are aimed at the treatment of neurogenic pain. The most frequently prescribed treatment is the tricyclic antidepressants, amitriptyline, desipramine, or nortriptyline. The latter two have a more favorable side effect profile with less sedation and anticholinergic effects. Documentation of a normal electrocardiogram (ECG) is recommended by some for patients over the age of 50. Dosage is started low, usually at 10 mg at night, and slowly titrated upward by 10 mg every one to two weeks until relief is achieved. Generally, if there is no relief at a dosage of 75 mg, treatment is discontinued. Patients must not stop tricyclics abruptly.

Gabapentin, an anticonvulsant, has been shown in small studies to provide pain relief for vulvodynia with fewer side effects than tricyclic antidepressants. Typical dosage is 100 mg at bedtime increased by 100 mg every two to seven days up to a maximum of 3,600 mg/day in divided doses. Side effects include nausea and sedation. In 2011, gabapentin was put on the Food and Drug Administration MedWatch list for a rare side effect, rhabdomyolysis. Patients should call their doctor regarding any muscle aches/pains or new-onset dark urine. A randomized controlled trial is ongoing.

Other medications used in the treatment of vulvodynia include pregabalin (titrated slowly to a maximum dose of 600 mg daily in divided doses), venlafaxine (37.5 mg initially to a maximum daily dose of 375 mg), and duloxetine (20–60 mg daily). None of these treatments have an evidence-based efficacy, and a high and potentially serious side effect profile limits their use.

Botox

Botulinum neurotoxin type A (Botox) injections into the vestibule seem to be a safe and effective treatment for provoked vestibulodynia. This treatment has been used in small numbers of women in two randomized trials. Botox is postulated to relieve both the muscular hyperactivity of the perineum and to reduce the pain through a blockage of the release of neuropeptides and neurotransmitters. Cost may prove to be a limiting factor of this treatment.

Physical Therapy

Patients with provoked vestibulodynia, compared to non-affected women, have pelvic floor muscle hypertonicity (increased tension), which may exacerbate the condition. Pelvic floor physical therapy has been shown to provide vulvovaginal pain relief and improve sexual functioning. Patients report physical, emotional, and sexual improvement with physical therapy, especially if it is part of a multifaceted treatment approach. Pelvic floor physiotherapists utilize internal and external soft tissue mobilization and massage, release of trigger points, biofeedback, and postural exercises.

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Updated Terminology and Classification of Vulvodynia

Two years ago, the boards of three prominent medical societies dedicated to women's health acknowledged the need to revise the definition and classification of vulvodynia to include recent research findings. To address this complex task, 35 representatives from the International Society for the Study of Vulvovaginal Disease (ISSVD), International Pelvic Pain Society, International Society for the Study of Women's Sexual Health and the NVA attended a two-day consensus conference in April 2015. The meeting, co-chaired by Drs. Andrew Goldstein, Jacob Bornstein and Denniz Zolnoun, consisted of multiple parts: (i) research and clinical presentations, (ii) division into six working groups to develop proposals, (iii) presentation of each working group's proposal to the entire group, (iv) selection of the most preferred proposal(s), and (v) a group effort, in which salient aspects of the top two proposals were combined to reach consensus on a final document.

Historical Perspective

In the 1980s, the term vulvodynia replaced "burning vulva syndrome". At that time, vulvodynia was simply defined as, "chronic vulvar pain of unknown cause, especially characterized by burning, stinging and rawness." In 2003, the ISSVD board expanded the definition of vulvodynia to, "Vulvar discomfort, most often described as burning pain, occurring in the absence of relevant physical findings or a specific, clinically identifiable neurologic disorder."

For many years, the two main subtypes of vulvodynia were *vulvar vestibulitis* ("itis" means inflammation) and *dysesthetic vulvodynia*. (Dysesthesia is an abnormal or painful sensation.) With the advent of research funding for vulvodynia, doctors and scientists became interested in studying vulvodynia, especially vulvar vestibulitis. Several researchers examined biopsies of vestibular tissue from these patients, but did not find signs of active inflammation, suggesting that vestibulitis was not an accurate diagnostic term. At the ISSVD's 2003 meeting, a new diagnostic scheme emerged, i.e., classification of vulvodynia was based on whether the pain was *localized* or *generalized*. The term *vestibulodynia* (pain in the vestibule), first used by Jacob Bornstein, M.D., replaced vulvar vestibulitis. The subtype previously known as dysesthetic vulvodynia was changed to *generalized vulvodynia*, defined as widespread pain in the vulva.

Consensus Terminology **Persistent Vulvar Pain and Vulvodynia**
Vulvar pain caused by a specific disorder • Infectious (e.g., herpes) • Inflammatory (e.g., lichen planus) • Hormonal (e.g., estrogen deficiency) • Neoplastic (e.g., Paget disease) • Neurologic (e.g., post-herpetic neuralgia) • Trauma (e.g., postoperative) • Iatrogenic (e.g., radiation)
Vulvodynia • Vulvar pain of at least three months duration, without a clear identifiable cause, which may have potential associated factors
Descriptors of vulvodynia • Localized (e.g., vestibulodynia, clitorodynia), generalized or mixed • Provoked (e.g., with intercourse, tampon insertion), spontaneous or mixed • Onset (primary or secondary) • Temporal pattern (constant, delayed, immediate, intermittent, persistent)

Differential Diagnosis

The challenge in diagnosing chronic vulvar pain is determining whether it is related to a specific disorder. In clinical practice, all identifiable causes of persistent vulvar pain must be ruled out prior to making a diagnosis of vulvodynia. Among the many disorders are recurrent Candida infection, skin disease (e.g., lichen sclerosus), nerve compression, squamous cell

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carcinoma, post-herpetic neuralgia, estrogen deficiency, obstetrical trauma, and cancer treatments. A thorough assessment should also test for systemic disorders that may cause vulvar pain, such as diabetes, Sjogren's syndrome and lupus. It is also possible for a woman to have a specific disorder that affects the vulva in addition to vulvodynia.

2015 Definition of Vulvodynia

At the consensus conference, the definition of vulvodynia was revised to incorporate recent advances in vulvodynia research. The 2015 definition is, "Vulvar pain of at least three months duration, without a clear identifiable cause, which may have potential associated factors." The phrase "without a clear identifiable cause" suggests that the cause(s) of vulvodynia are unclear, but that a physiological basis does exist. Often dismissed by thousands of doctors as a psychological condition, the current definition of vulvodynia may help to dispel that notion.

The updated definition also acknowledges that vulvodynia is a complex disorder, "which may have potential associated factors." Numerous studies have found a number of factors associated with vulvodynia. Among them are genetic abnormalities, hormonal deficiency, increased nerve fiber density in the vulvar vestibule, pelvic floor muscle hypertonicity, sexual dysfunction, central nervous system sensitization, and psychological conditions (e.g., depression and anxiety). Furthermore, studies have shown that a significant number of women with vulvodynia suffer from one or more comorbid pain disorders, such as irritable bowel syndrome, painful bladder syndrome, fibromyalgia and temporomandibular joint (TMJ) disorder.

Classification of Vulvodynia

As stated above, vulvodynia is first classified by the location of the pain, i.e., is the pain localized, generalized or mixed? Each subtype is further classified by the following pain characteristics: provocation, temporal pattern and onset. Does pain only occur when provoked or is it spontaneous (or both)? Is the pain constant or intermittent, immediate or delayed? When did the pain begin? If it occurred with the first tampon insertion or attempt at sexual intercourse, the patient has *primary* vulvodynia. If the pain occurred subsequent to a period of pain-free intercourse, the patient has *secondary* vulvodynia.

The majority of vulvodynia patients are diagnosed with provoked vestibulodynia, pain in the vestibule upon touch, pressure or penetration. Alternatively, women with generalized vulvodynia typically describe their pain as spontaneous and constant, although there may be occasional periods of relief.

Conclusion

The updated definition and classification of vulvar pain and vulvodynia reflect the progress that has occurred since the NIH, NVA and other institutions have been funding vulvodynia research. We are hopeful that the new terminology will encourage further research into the etiology of vulvodynia. The most clinically-relevant outcome of the 2015 terminology is that it underscores the many different presentations of vulvodynia and the importance of individualized multidisciplinary treatment.

(*Editor's note: See Bornstein et al, 2015 ISSVD, ISSWSH, and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia at www.nva.org/for-health-professionals/medical-journal-articles/.*)■

New Email Address?

The NVA is communicating more and more via email with our members. Please be sure to let us know if you have a new email address. Just send an email to Tamara Matos at admin@nva.org or call her at 301-299-0775. Thanks!

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Patients are provided with at-home exercises to help shorten the course of treatment. Medical professionals can provide instructional exams for patients to teach muscle relaxation and contraction and/or recommend physical therapy. Additionally, vaginal dilators are recommended, with or without physical therapy. No study has been carried out to evaluate the efficacy of physiotherapy in women with unprovoked vulvodynia. Spinal cord stimulation and transcutaneous electrical nerve stimulation are less frequently used to treat vulvodynia.

Counseling

Psychological, sexual and relationship disturbances are frequently encountered in vulvodynia patients. Often these conditions are secondary to the ongoing pain, and therapy is part of the multifaceted management of vulvodynia, either provoked or unprovoked. Cognitive behavioral therapy (CBT) that involves learning and practice of specific pain-relevant coping and self-management skills was shown to yield better outcomes and greater patient satisfaction in patients with vulvodynia than supportive psychotherapy. Additionally, CBT was shown to result in similar outcomes as electromyographic biofeedback and vestibulectomy, including significantly reduced pain and improved psychological adjustment and sexual function. Individual, couple, or sexual counseling should be recommended as appropriate. Again, the NVA is an excellent source for educational materials for these patients.

Surgery

Surgical management of vulvodynia has been advocated only for provoked vestibulodynia, and all experts agree that surgery should never be the first-line treatment. Many experts, however, do not recommend this treatment at all. Although a wide variety of surgical procedures have been advocated, randomized trials with appropriate short- and long-term outcome measures are lacking. Complete improvement of dyspareunia occurred globally in 60% of published studies. A recent meta-analysis of surgical outcomes for vestibulodynia estimated a 31–100% success rate with a median of 79% reporting partial to complete relief. There are no data looking at surgical outcomes in postmenopausal women.

Additional Treatment Options

The effect of acupuncture and other alternative therapies on pain and psychosexual adjustment requires further investigation. Local or regional nerve blocks have been shown in small studies to be effective in the treatment of vulvodynia. Combinations of anesthetics (lidocaine, bupivacaine) and steroids (triamcinolone acetonide, methylprednisolone) are infiltrated locally, via either a pudendal nerve block or caudal epidural injections. Repetitive treatments may be necessary.

Special Consideration of Menopausal Woman

All treatments for vulvodynia are off-label. In older women, there are potentially more risks with treatment than in their younger counterparts. Older patients are more likely to have chronic medical conditions, to be on one or more medications, or to be more affected by side effects, such as sedation or dry mouth/eyes. Slower upward titrations of medications and more frequent monitoring may be necessary. Primary care or specialist consultation should be sought as needed, especially prior to initiation of medications. Vulvovaginal atrophy is a condition secondary to the lack of estrogen, present in a large percentage of postmenopausal women. Local estrogen or nonhormonal moisturizers should be used to correct the VVA, which can be the only cause of introital dyspareunia or an aggravating factor in a patient suffering from provoked vestibulodynia. Estrogen therapy should be continued throughout vulvodynia treatment. Estrogen topical creams, vaginal inserts, or rings can be used.

Summary

Vulvodynia is a chronic and potentially debilitating

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pain condition. Though vulvodynia is more common during the reproductive years, there is clear evidence that this condition may affect menopausal women. The etiology of vulvodynia remains unknown, and evidence -based treatment options are not available. Little data exist on vulvodynia in menopausal or postmenopausal women; however, evidence suggests that menopausal changes may have an effect on chronic pain conditions. The management of vulvodynia in menopause should include a multifaceted approach with special attention to correcting estrogen deficiency and to the specific psychosexual and social context of menopause.

This article was excerpted with permission of Springer: Farage MA, Miller KW, Phillips N, Moyal-Barracco M, Ledger WJ. Vulvodynia in Menopause. In: Skin, Mucosa and Menopause. Date: 30 September 2014. Springer-Verlag Berlin Heidelberg; 2015. pp 275-84.

(Editor's note: To obtain the footnoted version of this article, with a full set of references, please contact Tamara Matos at admin@nva.org or 301-299-0775.)■

BIOMARKERS

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Pain is Complex

Once pain becomes chronic, it is no longer beneficial and becomes a disorder in and of itself. Chronic pain disorders may be broadly categorized as inflammatory, neuropathic or idiopathic (cause is unknown). Inflammatory pain disorders occur in response to tissue damage and infiltration of immune cells, while neuropathic pain disorders occur in response to nerve damage. Unlike inflammatory and neuropathic pain, idiopathic pain disorders are characterized by perpetual abnormalities in sensory processing that occur in the absence of direct inflammation or nerve damage, making them especially difficult to study and treat.

Vulvodynia is a common idiopathic pain disorder that often affects the vaginal, cervical, and/or deep pelvic regions. Unlike chronic vulvar pain related to inflammation (e.g., lichen sclerosus) or injury (e.g., postoperative nerve damage), the diagnosis of vulvodynia is based on the absence of organic pathology. Vulvodynia sometimes co-occurs with other idiopathic pain disorders including irritable bowel syndrome, temporomandibular disorder (TMD) and fibromyalgia (FMS). Accumulating evidence suggests that patients with comorbid conditions suffer from more severe pain and additional physical and psychological symptoms than those with vulvodynia alone. Despite the high prevalence of vulvodynia and its substantial negative impact on quality of life, current treatment regimens remain ineffective in most affected women because the causes of chronic pain are poorly understood and patients present with different clinical signs and symptoms reflective of their unique pain experience.

An individual's pain experience is as unique as her/his fingerprint — shaped by many factors, including the context surrounding the event, past experiences, stress level, belief systems, coping strategies and general health. When these factors are combined with individual variability in genes that regulate the development and function of the nervous system, immune response, and psychological mood, one quickly begins to appreciate the complex nature of pain. Identification of objective biological signatures or "biomarkers" that map onto distinguishing clinical features may help us understand the complex mechanisms underlying vulvodynia, and improve the current standard of care.

Biomarkers May Reduce Complexity

The National Institutes of Health *Biomarkers Definitions Working Group* defines a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a

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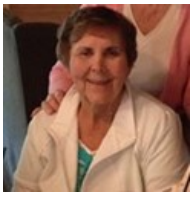
In Her Own Words

By Carol B



I am 75 years old and have led a very active life, including exercising five times a week, golfing, volunteering, and gardening. Several years ago I was diagnosed with lichen planus, a disease that can cause pain while sitting, but it did not affect my quality of life. Then, in February 2015, after driving eight hours to visit my daughter, suddenly I started experiencing severe pain that limited my activities. Thinking it was related to lichen planus, I went to my dermatologist. I was diagnosed with vulvodynia.

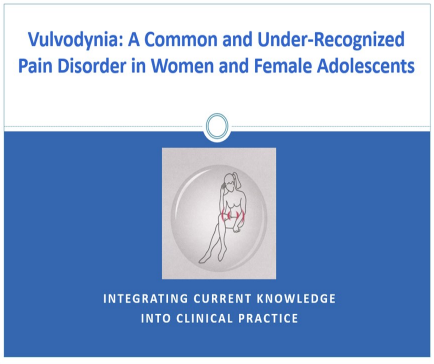
Since the diagnosis, I have had pain daily for seven months. I was treated with amitriptyline and gabapentin up to the highest tolerable doses. That gave me minor relief, but the side effects were as life-changing as the pain: extreme constipation, severe dry mouth, canker sores, and most significantly, loss of short-term memory and word retrieval in conversations. For four months I was unable to do any of the activities I previously enjoyed. Even sitting in church for an hour was extremely difficult.

I found a specialist at a large university hospital who confirmed the vulvodynia diagnosis and treatment. She ordered a few additional creams that made no difference and then suggested a pudendal block. My goal was to reduce the pain level to a five and resume a lifestyle I could manage. Sadly, after four different types of blocks, I had no relief and still had intense pain many days. I have learned to cope by managing the amount of time I sit each day, using some home remedies, trying to enjoy my garden, and making choices between activities I can tolerate.

Through months of independent research and the support of the NVA, I have found a vulvodynia clinic at another university hospital and we are starting over and working together to find the right balance of medications and dosages. I am slowly building my strength back up after being able to do very little for seven months. I'm beginning to sit and read, socialize and continue to garden. However, it is a very slow process. Some days the pain is a five and other days it goes up to a seven, even after light activity.

I was fortunate to be diagnosed quickly, but finding the right team of specialists to manage my treatment and my expectations has been a challenge. The NVA has been very helpful, encouraging me through this journey. My hope is that I will continue to get stronger and return to most of my daily activities with manageable pain. Throughout this process, I have educated many physicians, friends and family members about vulvodynia. I also want to help educate the medical community so others with this condition can find experts and relief much sooner than I did.■

NVA Releases Updated Online CME on Vulvodynia



The NVA is pleased to announce the release of its updated continuing education tutorial, *Vulvodynia: A Common and Under-Recognized Pain Disorder in Women and Female Adolescents — Integrating Current Knowledge into Clinical Practice*. We would like to extend our thanks to Drs. Jacob Bornstein, Andrew Goldstein, Colleen Kennedy Stockdale, Pamela Morrison Wiles and Ruby Nguyen for their contribution to this valuable educational tool. CME/CE accredited by Dannemiller, Inc. through March 2018, this tutorial incorporates the latest research results and covers all aspects of vulvodynia, including prevalence, etiology, differential diagnosis and treatment options. It can be accessed free of charge at cme.dannemiller.com/NVA-CE.

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therapeutic intervention. Potentially valuable biomarkers include those all along the canonical (well-established) pathway from gene (e.g., DNA) to phenotype (e.g., heart rate), with proteins being most commonly used. Proteins are the workhorses that carry out functions encoded by our genes and modified by our environment. Thus, proteins have proven to be robust molecular markers for a number of diseases.

Currently, protein biomarkers are used on a daily basis for the diagnosis, treatment and risk management of a number of prevalent health conditions. For example, circulating levels of glucose and glycated hemoglobin A1c are used to diagnose diabetes and predict full-blown diabetes. Blood tests for proteins such as troponin, creatine kinase and lactate dehydrogenase are routinely used in the diagnosis of coronary heart disease. Blood tests for cholesterol and coagulation factors, used to help determine the cause of a stroke, may influence treatment approaches. Finally, over 20 FDA-approved biomarkers are used in the prediction, diagnosis, monitoring and management of different cancers.

Although biomarkers for vulvodynia and other chronic pain disorders are not used clinically today, recent findings and ongoing work in this area suggest that hope is on the horizon. For the purpose of this article, emphasis will be placed on molecular biomarkers that represent potential candidates in the diagnosis of vulvodynia.

Candidate Protein Biomarkers for Vulvodynia

The human genome serves as a recipe for more than 20,000 proteins important for our development, basic cell function and overall health. Included in this recipe are hundreds of proteins known to influence factors relevant to chronic pain, including (i) the transmission of pain signals from nerves, (ii) the perception of pain by the brain, (iii) inflammatory responses to tissue injury and physiological stress, and (iv) psychological state. Of the hundreds of pain-relevant proteins, small intracellular proteins called cytokines have been the most widely studied in the pathophysiology of chronic pain. Cytokines are small intracellular regulatory proteins secreted by immune cells in the peripheral nervous system, and by neurons and glia in the central nervous system. In an acute setting, pro-inflammatory cytokines confer survival advantage by promoting immune responses that limit tissue damage and initiate healing. However, prolonged elevation of cytokines can cause sensory nerves to become over-excitable and amplify local pain signals. Numerous studies have shown that levels of pro-inflammatory cytokines are elevated in individuals with vulvodynia, as well as those with other idiopathic pain conditions, such as TMD and FMS. Over the years, work by David Foster and others has shown that levels of the classical pro-inflammatory cytokines, tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8), are elevated in local biopsy samples collected from women with vulvodynia compared to pain-free controls. Levels of these pro-inflammatory cytokines also are elevated in the temporomandibular joints of TMD patients and found to correlate with greater pain, stress and depressed mood.

Sustained peripheral inflammation can lead to neuroplastic changes in the spinal cord and brain, such that pain signals become amplified at regions remote from the original painful site. Whereas the local effects of cytokines are highly relevant to the study of purely site-specific idiopathic pain disorders, it is likely that more generalized systemic processes contribute to comorbid pain disorders. Thus, in addition to being easy to obtain, protein biomarkers in the blood may better capture systemic abnormalities in pain and inflammation. In a recent paper by Brittney Ciszek and colleagues, different patterns of circulating cytokines differentiated women with vulvodynia alone from those with comorbid idiopathic pain conditions. Specifically, women with vulvodynia alone had increased expression of the pro-inflammatory cytokine IL-8 and the anti-inflammatory cytokine IL-1ra. In contrast, women with vulvodynia and comorbid pain disorders

(*See BIOMARKERS, page 11*)

had increased expression of the pro-inflammatory cytokine IL-8, with no compensatory increase in the anti-inflammatory cytokine IL-1ra. Similar imbalances between IL-8 and IL-1ra occur in individuals with TMD who also have widespread pain. Abnormalities in levels of pro-inflammatory cytokines are often accompanied by alterations in levels of anti-inflammatory cytokines that keep inflammation under control and maintain homeostasis. These findings suggest that women with vulvodynia and pain at other sites have more severe impairment in anti-inflammatory responses.

Further studies are needed to screen additional proteins linked to biological pathways that influence pain transmission, psychological state and inflammatory response. Currently underway, this work is using a new protein microarray technology to simultaneously measure the levels of hundreds of proteins in samples collected from women with vulvodynia and comorbid pain disorders.

Candidate Gene Biomarkers for Vulvodynia

The primary function of genes is to make proteins that determine everything about us — from the color of our eyes to how we behave in the environment. Each gene is composed of a specific sequence of nucleic acids that specifies the sequence of amino acids in the corresponding protein. Mutations or variations in genetic sequence may sometimes lead to abnormalities in proteins that influence an individual's response to her/his environment, such as pain level following trauma or stress.

With advances in genotyping methods, the list of genes associated with chronic pain disorders is rapidly increasing. With rare disorders, such as congenital insensitivity to pain, a single variant in a single gene can produce dramatic effects on pain perception. Patients with congenital insensitivity to pain have specific mutations in the nerve growth factor gene critical for the survival of sensory nerves and, thus, suffer from an inability to sense pain, temperature or touch. In contrast, common complex chronic pain disorders, such as vulvodynia, are influenced by a diverse set of environmental events (e.g., trauma and stress) and an array of genetic variants.

Association studies of vulvodynia have largely focused on genetic variants in immune pathways because of the previously established relationship with cytokines. Studies by Stefan Gerber, Steven Witkin and colleagues have demonstrated that variants in genes encoding IL-1β and IL-1ra are risk factors for vulvodynia. In addition, these variants were shown to be predictive of clinical (e.g., time of onset) and biological (e.g., inflammatory response) patient characteristics. A genetic variant in a protein that regulates IL-1β production was able to differentiate subsets of vulvodynia patients based on history of recurrent vulvovaginal candidiasis. A genetic variant in mannose-binding lectin (MBL), an innate immunity protein, was associated with vulvodynia and found to produce a 10-fold reduction in MBL plasma protein levels. These data reveal the importance of genetic susceptibility to pathologic immune responses, which may play a key role in vulvodynia.

Genetic variants in non-immune pathways have also been shown to predict vulvodynia risk. A particular genetic variant in melanocortin-1 receptor (MC1R), associated with red hair and fair skin, was shown to be more common in women with vulvodynia. Finally, a recent study by Andrew Goldstein and colleagues found a genetic variant in the androgen receptor to be predictive for the development of vulvodynia among women taking combined hormonal contraceptives. Although these studies have identified candidate variants that may play a significant role in vulvodynia, many more genetic variants are likely involved and need to be explored.

Epigenetic Biomarkers for Vulvodynia

In addition to direct changes in nucleic acid sequence, genes can be turned on or off by external or environmental events known as epigenetic factors. These

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factors, including toxins, medications, diet, psychological stressors, age and nutrition, can stimulate biological processes in cells (e.g., DNA methylation, histone acetylation, RNA interference, and microRNAs). Epigenetic factors may be critical in the development of chronic pain disorders, as they can control the expression of genes involved in pain and inflammation.

MicroRNAs (miRNAs) represent one type of epigenetic regulation recently explored in vulvodynia. They are small, non-protein coding pieces of RNA that inhibit gene expression by binding to corresponding messenger RNAs (mRNAs), transcripts that contain genetic information to be translated into proteins. It is estimated that up to one-third of all protein-coding genes are regulated by microRNAs. Emerging evidence implicates miRNAs in the regulation of molecular pathways linked to pain, inflammation and immune response. Differential expression of miRNAs in chronic pain conditions has been reported in both local affected tissue and systemic blood. A recent preclinical study on neuropathic pain reported a positive correlation between pain thresholds and miR-30c levels in plasma and cerebrospinal fluid. A clinical study on regional pain syndrome identified 18 miRNAs differentially expressed in blood.

In the study by Ciszek and colleagues, the expression of 750 miRNAs was evaluated in women with vulvodynia. Researchers found that patients with vulvodynia alone displayed a dysregulation of 10 microRNAs important for pain and estrogen signaling. Meanwhile, patients with vulvodynia and comorbid pain disorders displayed dysregulation of 11 miRNAs important for pain, cell physiology and insulin signaling. MicroRNA expression was correlated with pain-relevant phenotypes and cytokine levels.

These findings suggest miRNAs represent a valuable tool for differentiating two vulvodynia subtypes: (i) localized pain with focal peripheral sensory disruption and (ii) widespread pain with a central nervous system dysregulation. Tests using miRNAs as biomarkers are commercially available for diagnosis of cancers, and may one day serve as screening tools for vulvodynia and related chronic pain disorders.

Conclusion

Current treatment regimens for vulvodynia remain largely ineffective because the causes of chronic pain are poorly understood and patients present with different clinical signs and symptoms. Two patients may share the same diagnosis, but have reached that diagnosis by walking down very different paths. One patient may have developed the disorder due to genetic variation in genes that regulate sensory nerve function, while another patient developed the disorder due to the presence of genetic variants that predisposed her towards increased inflammatory stress responses and heightened awareness of pain.

Identifying the most logical treatment procedure for each patient (e.g., pelvic floor muscle therapy, nerve block and/or administration of anti-inflammatory or anti-anxiety medication) will require an understanding of each individual's molecular genetic features in addition to her clinical characteristics. With continued research in biomarker discovery, we will gain an understanding of these molecular differences, enabling us to develop individualized treatment strategies.

(Editor's note: To obtain the footnoted version of this article, with a full set of references, please contact Tamara Matos at admin@nva.org or 301-299-0775.)■

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