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A deficiency in interferon-alpha production in women with vulvar vestibulitis.

Gerber S, Bongiovanni AM, Ledger WJ, Witkin SS

Am J Obstet Gynecol 2002 Mar;186(3):361-4

OBJECTIVE: Previous studies have suggested that interferon-alpha may be an effective treatment for some women with vulvar vestibulitis. We evaluated whether women with this syndrome had a deficiency in endogenous and induced interferon-alpha production. STUDY DESIGN: Blood was collected in heparinized tubes from 62 women with vulvar vestibulitis and 47 control women of similar age and ethnicity. Whole blood cultures were incubated in the presence of 0.1 ng/mL lipopolysaccharide (induced) or culture medium (uninduced) for 18 to 20 hours. Aliquots were tested for interferon-alpha levels by enzyme-linked immunosorbent assay. Vestibular samples were tested for human papillomavirus by polymerase chain reaction. Aliquots were also characterized for alleles of the polymorphic gene, interleukin-1 receptor antagonist, by polymerase chain reaction. RESULTS: In uninduced cultures, interferon-gamma was present in 68.1% of control subjects as opposed to 33.9% of vulvar vestibulitis patients (P =.0005). Similarly, after lipopolysaccharide stimulation, 70.2% of control subjects and only 48.4% of patients produced interferon-alpha (P=.03). Among the positive samples, however, there were no differences in the interferon-alpha levels between patients and control subjects. In contrast, induction of interferon gamma in response to lipopolysaccharide was similar in control subjects (78.0%) and vulvar vestibulitis patients (82.1%). Women who have a deficiency in interferon-alpha production did not have an increased prevalence of human papillomavirus infection. There was no relation between interleukin-1 receptor antagonist genotype and interferon-alpha production. CONCLUSION: An inability to produce interferon-alpha may contribute to chronic vestibular inflammation in some women.

Defective regulation of the proinflammatory immune response in women with vulvar vestibulitis syndrome.

Gerber S, Bongiovanni AM, Ledger WJ, Witkin SS

Am J Obstet Gynecol 2002;186:696-700

Objective: The cause of vulvar vestibulitis syndrome is unknown. To determine a possible role for defective immune regulation in this chronic condition, proinflammatory and anti-inflammatory immune responses to the 70-kd heat shock protein and to lipopolysaccharide were compared in women with and without vulvar Vestibulitis syndrome. Study design: Whole blood cultures from 62 women with vulvar vestibulitis syndrome and 48 control subjects were incubated in the presence or absence of 5 µg/mL human recombinant 70-kd heat shock protein or 0.1 ng/mL lipopolysaccharide for 18 hours. The culture supernatants were then assayed for interleukin-1 and interleukin-1 receptor antagonist by enzyme-linked immunosorbent assay. Results: Median levels of interleukin-1 were higher in response to heat shock protein in cultures from patients with vulvar vestibulitis syndrome (median, 1.07 ng/mL) as opposed to control subjects (median, 0.40 ng/mL; P= .006). Conversely, levels of interleukin-1 receptor antagonist were higher in response to heat shock protein in control subjects (median, 39.21 ng/mL) than in patients (median, 29.25 ng/mL; P = .009).In response to lipopolysaccharide, median levels of interleukin-1 were similar in patients (1.00 ng/mL) and control subjects (1.15 ng/mL); median interleukin-1 receptor antagonist concentrations were higher in control subjects (70.0 ng/mL) than in patients (44.3 ng/mL; P< .0001). The ratio of interleukin-1 receptor antagonist to interleukin-1 was higher in control subjects than in women with vulvar Vestibulitis syndrome in response to both heat shock protein (P= .0002) and lipopolysaccharide (P= .01). In uninduced cultures, interleukin-1 receptor antagonist levels were also higher in control subjects (median, 1.60 ng/mL) than in patients with vulvar vestibulitis syndrome (median, 0.62 ng/mL; P< .0001). Conclusion: A relative inability to down-regulate proinflammatory interleukin-1 activity by interleukin-1 receptor antagonist may contribute to the pathophysiologic features of vulvar vestibulitis syndrome.

Vestibular tactile and pain thresholds in women with vulvar vestibulitis syndrome.

Pukall CF, Binik YM, Khalife S, Amsel R, Abbott FV

Pain 2002 Mar;96(1-2):163-75

Vulvar vestibulitis syndrome (VVS) is a common cause of dyspareunia in pre-menopausal women. Little is known about sensory function in the vulvar vestibule, despite Kinsey's assertion that it is important for sexual sensation. We examined punctate tactile and pain thresholds to modified von Frey filaments in the genital region of women with VVS and age- and contraceptive-matched pain-free controls. Women with VVS had lower tactile and pain thresholds around the vulvar vestibule and on

the labium minus than controls, and these results were reliable over time. Women with VVS also had lower tactile, punctate pain, and pressure-pain tolerance over the deltoid muscle on the upper arm, suggesting that generalized systemic hypersensitivity may contribute to VVS in some women. In testing tactile thresholds, 20% of trials were blank, and there was no group difference in the false positive rate, indicating that response bias cannot account for the lower thresholds. Women with VVS reported significantly more catastrophizing thoughts related to intercourse pain, but there was no difference between groups in catastrophizing for unrelated pains. Pain intensity ratings for stimuli above the pain threshold increased in a parallel fashion with log stimulus intensity in both groups, but the ratings of distress were substantially greater in the VVS group than in controls at equivalent levels of pain intensity. The data imply that VVS may reflect a specific pathological process in the vestibular region, superimposed on systemic hypersensitivity to tactile and pain stimuli.

Postherpetic neuralgia after shingles, an under-recognized cause of chronic vulvar pain.

Oaklander AL, Rissmiller JG

Obstet Gynecol 2002 Apr;99(4):625-8

BACKGROUND:Vulvar shingles, an uncommon presentation of a common disease, probably affects 1.5 million American women during their lifetime and leaves about 150,000 with postherpetic neuralgia, a chronic neuropathic pain syndrome. Prompt diagnosis and treatment can minimize pain severity and duration.CASES:The case of an 88-year-old woman with sacral shingles is described. Complications led to her demise. A 35-year-old with a 6-year history of disabling vulvar pain and many diagnostic procedures was ultimately diagnosed with postherpetic neuralgia. CONCLUSION:Shingles needs to be included in the differential diagnosis of vulvar rashes because it is a modifiable risk factor for chronic vulvar pain. The possibility of postherpetic neuralgia must be considered in women with unexplained vulvar dysesthesia.

Physical therapy for vulvar vestibulitis syndrome: a retrospective study.

Bergeron S, Brown C, Lord MJ, Oala M, Binik YM, Khalife S

J Sex Marital Ther 2002 May-Jun;28(3):183-92

This retrospective study evaluated the effectiveness of physical therapy in relieving painful intercourse and improving sexual function in women diagnosed with vulvar vestibulitis. This syndrome is a frequent cause of premenopausal dyspareunia and is characterized by a sharp, burning pain located within and limited to the vulvar vestibule (vaginal entry) and elicited primarily via pressure applied to the area. Participants were 35 women with vulvar vestibulitis who took part in physical therapy treatment for an average of 7 sessions. We

conducted telephone interviews to assess whether physical therapy or other subsequent treatments impacted on pain during intercourse and sexual functioning. Length of treatment follow up ranged from 2 to 44 months, with a mean of 16 months. Physical therapy yielded a complete or great improvement for 51.4% of participants, a moderate improvement for 20.0% of participants, and little to no improvement for the other 28.6%. Treatment resulted in a significant decrease in pain experienced both during intercourse and gynecological examinations; it also resulted in a significant increase in intercourse frequency and levels of sexual desire and arousal. Successful patients were significantly less educated than nonsuccessful patients. Findings demonstrate that physical therapy is a promising treatment modality for dyspareunia associated with vulvar vestibulitis.

Burning mouth syndrome and vulvodynia coexisting in the same patient: a case report.

Gaitonde P, Rostron J, Longman L, Field EA

Dent Update 2002 Mar;29(2):75-6

The 'dynias' are a group of chronic focal pain syndromes with a predilection for the orocervical and urogenital regions. This is a case report of stomatodynia (burning mouth syndrome) and vulvodynia coexisting in a middle-aged woman. The dynias are an enigma in terms of aetiology, which is multifactorial, making clinical investigations difficult and often requiring liaison with other specialties.

Botulinum toxin A for generalized vulvar dysesthesia.

Gunter J, Brewer A

Abstract: American Pain Society Annual Meeting, Baltimore, MD, March 14-17, 2001

Published in: The Journal of Pain, Vol 3, Num 2, Sup 1, April 2002, pg 21

In this case, a 22-year old woman had a 4-year history of generalized vulvar dysesthesia and severe dyspareunia. Q-tip examination revealed severe, diffuse allodynia of the vulva with associated muscular spasm of the perineal body. Insertion of a vaginal speculum produced severe pain. The patient was unable to tolerate biofeedback therapy and amitriptyline. Her pain was refractory to multiple topical therapies, oral gabapentin, and carbamazepine. She had no improvement in her pain with the following: two local injections of bupivicaine and triamcinolone, a bilateral pudendal block with bupivicaine and triamcinolone, and two caudal epidural injections of steroid and bupivicaine. As her pain was generalized, extending beyond potential resection margins for a vestibulectomy, she was offered a trial of botulinum toxin A. Ten units of botulinum toxin A were injected into the muscles of the perineal body beneath the posterior fourchette; 5 units each were injected approximately 1 cm from the midline. At 2

weeks the patient was able to tolerate insertion of a speculum with minimal discomfort and at 4 weeks post injection the pain had become localized to the hymen and posterior fourchette with improvement of the associated muscle spasm; her dyspareunia, however, persisted. As the pain was now localized to the vestibule, the patient opted for a vestibulectomy that was performed without complication. At 8 weeks post-operatively the patient was pain free on exam and able to tolerate vaginal intercourse. Botuliinum toxin A is effective in the treatment of many dystonias and has been used for vulvar dysesthesia. We believe that the partial response experienced by this patient may be due to inadequate dosing. We are encouraged by this initial report and are currently investigating boltulinum toxin A for vulvar dysesthesia in a phase II trial.

Strategies required to improve the management of chronic vulvar discomfort in Australia.

Wines N

Aust N Z J Obstet Gynaecol 2002 Feb;42(1):75-8

OBJECTIVE: To investigate factors required to improve the management of vulvar pain from a patient perspective. SAMPLE AND SETTING: Sixty patients in four different specialised vulvar clinics. METHODS: Women with chronic vulvar pain were asked to complete a questionnaire whilst waiting for specialist consultation by either a dermatologist, sexual health physican, psychologist or physiotherapist. RESULTS: The average length of time patients had vulvar pain was 6.03 years, with a mean of 5.83 practitioners seen. Twenty-seven per cent indicated that increased awareness of vulvodynia was required by gynaecologists and 74% suggested that increased general practitioner awareness was necessary to improve care. Accurate diagnosis, and understanding lifestyle implications were key elements of patient satisfaction, considered more important than any available treatment modality. CONCLUSIONS: Current services and skilled practitioners available for the management of chronic vulvar pain or vulvodynia in Australia do not reflect the estimated prevalence of this condition. From this study it was concluded that the three most important factors required to improve quality of care in order of importance were increased practitioner awareness, research and the setting up of more specialised multi-disciplinary clinics.

Pelvic disorders in women: chronic pelvic pain and vulvodynia.

Newman DK

Ostomy Wound Manage 2000 Dec;46(12):48-54

Chronic pelvic pain and vulvodynia are frustrating pelvic disorders seen in young adult women. In the medical literature, these two conditions are linked together under the category of "chronic pelvic pain syndromes." Underlying pathophysiology is not well understood, and relatively scant research is available on successful treatment options.

Patients often seek the help of specialists who provide nonsurgical treatments for incontinence and related pelvic disorders. This article provides an overview of the clinical presentation of both chronic pelvic pain and vulvodynia. Specific evaluation techniques, including abdominal, pelvic, bimanual rectal-vaginal, and neurologic examinations, are described. Several practical treatments, such as dietary interventions, vitamin supplementation, muscle relaxation training, biofeedback therapy, and electrical stimulation are discussed as options in a private practice setting.

Clitoral pain: the great unexplored pain in women.

Gordon AS

J Sex Marital Ther 2002;28 Suppl 1:123-8

Clitoral pain is not often reported by patients or in literature. The author reports on 7 women from his practice and 14 women who were on-line volunteers, all of whom had clitoral pain as a major feature. Features included mild to moderate rest pain and significant contact, light-touch induced or pressure induced pain. Associations include Multiple Sclerosis, GUillain Barre Syndrome, urethral sphincter dyssynergia, various vulvar pain syndromes (nine cases), post-hysterectomy, Lichen Sclerosis (five cases), spondylolisthesis, vaginismus and genital or pelvic trauma. Eight claimed painful, allodynic nipples and seven had sensitive nipples. Clitoral pain was an important cause of pain in these women.

Vulval disease from the 1800s to the new millennium.

Lewis FM

J Cutan Med Surg 2002 Apr 15

Background: The study of vulval disease has become important over the last few decades. Although several inflammatory dermatoses were described at the end of the 19th century, vulval involvement in these conditions was only realized some time later. Indeed, the vulva may be a site of predilection of some inflammatory dermatoses such as lichen sclerosus. Objective: There are now groups of interested dermatologists, gynecologists, and genitourinary physicians that have cooperated to study patients with vulval disease. Hopefully, this will increase our knowledge over the next century. Conclusion: This review article examines vulval disease from an historical viewpoint and highlights important developments that have increased our understanding of the disorders that specifically affect the vulva.

Vulvar pain may signal cancer.

[No Authors Listed]

AWHONN Lifelines 2001 Jun-Jul;5(3):19

Support group helps women with vulvodynia.

Wade M

Nurs N Z 2000 Mar;6(2):17-9

Differentiation between women with vulvovaginal symptoms who are positive or negative for Candida species by culture.

Linhares L M, Witkin S S, Miranda S D, Fonseca A M, Pinotti J A, Ledger W J

Infect Dis Obstet Gynecol 2001;9(4):221-5

OBJECTIVE: To investigate whether clinical criteria could differentiate between women with vulvovaginitis who were culture positive or negative for vaginal Candida species. METHODS: Vulvovaginal specimens were obtained from 501 women with a vaginal discharge and/or pruritis. Clinical information and wet mount microscopy findings were obtained. All specimens were sent to a central laboratory for species identification. RESULTS: A positive culture for Candida species was obtained from 364 (72.7%) of the specimens. C. albicans was identified in 86.4% of the positive cultures, followed by C. glabrata in 4.5%, C parapsilosis in 3.9%, C. tropicalis in 2.7% and other Candida species in 1.4%. Women with a positive Candida culture had an increased utilization of oral contraceptives (26.1% vs. 16.8%, p = 0.02) and antibiotics (8.2% vs. 0.7%, p = 0.001), and were more likely to be pregnant (9.1% vs. 3.6%, p = 0.04) than the culture-negative women. Dyspareunia was more frequent in women without Candida (38.0% vs. 28.3%, p = 0.03) while vaginal erythema (p = 0.01) was more common in women with a positive Candida culture. CONCLUSIONS: Although quantitative differences were observed, the presence of vaginal Candida vulvovaginitis cannot be definitively identified by clinical criteria.

New immunotherapeutic strategies to control vaginal candidiasis.

Magliani W, Conti S, Cassone A, De Bernardis F, Polonelli L.

Trends Mol Med 2002 Mar 1;8(3):121-6

The widespread occurrence of mucosal infections caused by Candida, in particular recurrent vulvovaginal candidiasis among fertile-age women, together with the paucity of safe candidacidal antimycotics, have prompted a great number of investigations into the immunotherapy of candidal vaginitis. This article will discuss three different experimental approaches demonstrated to be potentially transferable to human disease: (1) the use of antibodies against well-defined cell-surface adhesins or enzymes; (2) the generation of yeast killer-toxin-like candidacidal anti-idiotypic antibodies and their engineered

molecular derivatives (e.g. single chains, peptides); and (3) the generation of therapeutic vaccines and immunomodulators.

Intravaginal and intranasal immunizations are equally effective in inducing vaginal antibodies and conferring protection against vaginal candidiasis.

De Bernardis F, Boccanera M, Adriani D, Girolamo A, Cassone A

Infection and Immunity, May 2002, p. 2725-2729, Vol. 70, No. 5

Oophorectomized, estrogen-treated rats were immunized by the intravaginal or intranasal route with a mannoprotein extract (MP) or secreted aspartyl proteinases (Sap) of Candida albicans, with or without cholera toxin as a mucosal adjuvant. Both routes of immunization were equally effective in (i) inducing anti-MP and anti-Sap vaginal antibodies and (ii) conferring a high degree of protection against the vaginal infection by the fungus. These data suggest that appropriate fungal antigens and adjuvant can be used to protect against candidal vaginitis, by either route.

Candida lusitaniae as an unusual cause of recurrent vaginitis and its successful treatment with intravaginal boric acid.

Silverman N S, Morgan M, Nichols W S

Infect Dis Obstet Gynecol 2001;9(4):245-7

Increasing use of short-course antifungal therapies in patients with recurrent vulvovaginitis may enable the emergence of less-common, more resistant yeast strains as vaginal pathogens. We report the case of a patient with chronically symptomatic and repeatedly treated vaginal candidiasis whose infection was attributable to Candida lusitaniae, a previously unreported cause of candidal vaginitis.

New antidepressants in the treatment of neuropathic pain. A review.

Mattia C, Paoletti F, Coluzzi F, Boanelli A

Minerva Anestesiol 2002 Mar;68(3):105-14

Before 1980s, tricyclics (TCAs) were considered, between antidepressants, the standard in the treatment of different kinds of neuropathic pain, for their action on noradrenergic and serotoninergic pathways, thought the high incidence of side effects. In 1980s a new class of antidepressants has been introduced, the selective serotonin reuptake inhibitors (SSRI). We reviewed some publications, including trials comparing SSRIs with TCAs in pain management. The available literature did not show an effective superiority of the former on the latter, though improved side-effect profile. Recently new antidepressants were introduced in the clinical use, with a significant

reduction in side effects and equivalent efficacy on mood disorders. These new drugs may be classified in three categories: Serotonin and Noradrenergic Reuptake Inhibitors (SNaRI), like venlafaxine and nefazodone; Noradrenergic and Specific Serotoninergic Antidepressants (NaSSA), like mirtazapine, and Noradrenaline Reuptake Inhibitors (NaRI), like reboxetine. In this review we present the available publications of their application in the treatment of neuropathic pain. Venlafaxine (SNaRI), the most investigated of these new drugs, was shown to be effective in the treatment of different kinds of pain, with side-effects profile significantly better than TCAs. The other new antidepressants have been less extensively studied, thus only anecdotal therapeutic results and experimental works have been found and reported. Existing data are surely insufficient to conclude which of these new classes of drugs has the best clinical profile and can be more effective in the treatment of neuropathic pain, but the lower incidence of side effects should be considered. Further evidence-based research in the safety and efficacy of these promising agents in pain relief, is warranted.

Why are substance P (NK1)-receptor antagonists ineffective in pain therapy?

Herbert MK , Holzer P

Der Anaesthesist, Volume 51 Issue 4 (2002) pp 308-319

The undecapeptide substance P is expressed by primary afferent neurons where it is considered to be a cotransmitter of other peptides and glutamate. Since it is predominantly found in sensory neurons with unmyelinated fibres (C-fibres), substance P has long been thought to be a "pain transmitter". Following stimulation of nociceptive afferents, substance P is released in the spinal cord and substance P-mediated transmission is prima-rily brought about by tachykinin NK1 receptors. To inhibit this process, a considerable number of non-peptide, highly potent, highly selective and brain penetrant NK1 receptor ant-agonists have been developed during the past decade. Experimental studies have proved that NK1 receptor antagonists are indeed able to blunt pain in sensitized states and thus to reverse hyperalgesia, whereas acute pain is left fairly unchanged. The hyperalgesic role of substance P has been corroborated by the sensory deficits seen in substance P and NK1 receptor knockout mice. However, the concept that NK1 receptor antagonists would represent a novel class of analgesic drugs, as suggested by the preclinical studies, has not been borne out by the clinical trials that have been reported thus far. This article offers an overview of those hyperalgesic conditions in which NK1 receptor antagonists may be of therapeutic value and discusses possible easons for the discrepancies between preclinical and clinical trials with NK1 receptor antagonists.

Vaginal hyperalgesia in a rat model of endometriosis is greatest in proestrus.

Cason A, Berkley K

Abstract: American Pain Society Annual Meeting, Baltimore, MD, March 14-17, 2001

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Surgical induction of endometriosis in rats decreases fertility and gives rise to vaginal hyperalgesia (1). Here we examined how estrous stage influences this hyperalgesia. Subjects were 9 virgin female Sprague-Dawley rats with regular 4-day estrous cycles, trained to escape vaginal distention produced by inflation of latex balloons. Percent escape responses to different volumes of distention, and vaginal pressures produced by those volumes were measured for ~2.5 months before and ~2.5 months after endometriosis (n=5) or sham surgery (n=4) in each of each rat's four estrous stages: proestrus, estrus, metestrus, and diestrus. Surgical induction of endometriosis, under ketamine/xylazine anesthesia, involved autotransplantation of small pieces of uterus on alternate mesenteric cascade vessels, abdominal wall, and one ovary. Sham surgery was identical, with autotransplantation of fat instead of uterine tissue. Escape responses to vaginal distention were significantly increased ($p<0.05$) in rats whose autotransplants had formed endometriotic cysts but were unchanged in rats whose autotransplants had not formed cysts. This vaginal hyperalgesia was significant, however, only when the rats were in proestrus ($p<0.02$) – an estrous stage during which estradiol and progesterone levels are rapidly increasing. There were no significant changes in vaginal pressures. The vaginal hyperalgesia produced by surgical endometriosis may involve a hormonally-exacerbated process in which sensitized sensory afferents innervating regions near the abdominal cysts sensitize neurons within the central nervous system that receive converging information from the vaginal canal; ie, a process of hormonally modulated viscero-visceral referred hyperalgesia.

1. Berkley KJ, Cason A, Jacobs H, Bradshaw H, Wood E. Vaginal hyperalgesia in a rat model of endometriosis. Neurosci Lett 306 (2001) 185.

Interaction between pelvic and pudendal afferent inputs in lumbar-sacral spinal cord in rats.

Wang RP, Li QJ, Lu GW

Sheng Li Xue Bao 2000 Apr 25;52(2):115-118

Time-dependent inhibition is one of the means to study the interactions between peripheral inputs. The present study was performed on anesthetized and paralyzed Wistar rats using the technique of conditioning-testing stimulation. Electric stimulation (1.5 3 folds of the threshold intensity) was given to pelvic and pudendal nerves. Extracellular recordings were made from convergent neurons at L(6)-S(1) segments of the spinal dorsal horn. Stimulus intervals between conditioning and testing stimulation were measured when a half of the testing responses were inhibited by conditioning responses or the inhibition just began to occur. The time-dependent inhibition was seen

in neurons situated deeper than 300 m beneath the dorsal surface of the spinal cord, and not in more superficial neurons. The inhibition intervals were in the range of 1 360 ms and became longer when conditioning stimulation was given to the pelvic nerve. The inhibition intervals were 1 3 ms in superfical neurons (<300 &mgr;m) and no apparent time-dependent inhibition occurred. The inhibition in deeper neurons was partially reduced by cold block conducted at segments C(5-6) and the blockage was more significant when conditioning stimulation was applied to the pelvic nerve. These findings suggest that the inputs from the pelvic and pudendal nerves may converge on single neurons at deeper lumbosacral dorsal horn and the pudendal nerve induced responses are more likely to be inhibited in these neurons, which may be further strengthened by superspinal structures.