Vulvar Pain Mechanisms

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1. Describe clinical characteristics of vulvodynia
2. Explain potential pain mechanisms
3. Examine etiological hypotheses (\(H_{VDN}\))
4. Evaluate experimental mouse model of vulvodynia
5. Overview and conclusions
Definitions and Critiques

Chronic vulvar pain without an identifiable cause

Generalized

Localized

- Provoked
- Unprovoked
- Mixed

(Edwards, 2004)

Multiple etiological pathways are suspected:
- nonspecific inflammation
- clinical distinctions between primary and secondary VDN
- comorbidities with other pelvic and non-pelvic pain
- variance in pain onset, intensity, frequency, treatment success
Vulvodynia: Impact on Quality of Life

Vulvodynia

Interpersonal
- Trust
- Intimacy
- Guilt
- Showing Affection

Sexual Dysfunction
- Pain with Sex
- Desire
- Arousal
- Satisfaction

Daily Function
- Sitting
- Standing
- Exercising
- Sleep
- Hobbies

Psychological
- Shame
- Anxiety
- Depression
- Fear
- Distress

Vulvodynia

Ponte et al., 2009
• Peripheral versus central nervous systems
  - Nociceptor sensitization
  - Spinally-mediated sensitization
  - Enduring brain gray matter changes

• Initiation versus maintenance factors
  - inflammation may initiate pain, yet central factors may perpetuate pain
Abnormal Pain Transmission to Brain

Peripheral Sensitization

Noxious Vulvar Stimulation

Central Sensitization

Neuroplasticity

Herrero & Cervero, 1996
Genital Sensitivity

Cutaneous AND visceral vulvovaginal structures are affected

Vulvar Hyperalgesia

Vaginal Allodynia

Controls

PVD

Controls

PVD

Force (g)

Dilator Volume (cc)

r = 0.59

r = 0.0

r = 0.77*

r = 0.66*
Innate Immunity
Begins 0-4 hrs
Fully engaged in 4 days

Adaptive Immunity
Begins within 5-7 days
Acute Inflammation

\[ H_{VDN} \]

Interferon alpha

\[ \uparrow \text{Interleukin 1}\beta \]

Inhibited viral recognition (failure to mount inflammatory cascade needed to defend body)

Innate Immunity

Adaptive Immunity
Infection = [Tissue invasion by pathogens] that cause [tissue injury]

Pathogen Properties

- Type
- Number
- Virulence

Host Response

- De novo inflammation
- AND
- Previous exposures - Vulnerability to pathogens - Immune suppression - Hormonal milieu -
Genes: Innate Immunity $H_{VDN}$

**Genetic vulnerabilities**
- Cytokines (i.e., interleukins)
- Proteins (i.e., mannose binding lectin)

- Deficient mannose-binding lectin (MBL) expression in primary VDN *(poor recognition of pathogens)*
- NALP3 (allele 7), regulates IL-1β production *(may result in reduced IL-1β and inhibit gene expression related to inflammation)*
- Melanocortin receptor 1 (MC1R) influences inflammatory cascade
  - Interleukin 1 receptor antagonist (IL1RN) polymorphisms – extended inflammation
Innate Immune Response

Genetic vulnerabilities
- Cytokines (i.e., interleukins)
- Proteins (i.e., mannose binding lectin)

Adaptive Immune Response

Estrogens

Altered Innervation
- gross innervation
- peptidergic afferents
- heat-sensing afferents
Pelvic Floor Muscle $H_{VDN}$

Muscular:
- Hypertonicity
- Instability
- Weakness

Perceived threat is positively correlated with EMG vaginal activity in healthy and vaginismus women

(Van der Velde & Everaerd, 2001)

Cause or consequence?
Hormonal $H_{VDN}$

Estrogen has widespread local and systemic effects that influence pain

Estrogen replacement reverses ovariectomy-induced vaginal hyperalgesia

Bradshaw & Berkeley, 2002

Provoked VDN is associated with lower estrogen receptor $\alpha$ in vulvar tissue

Eva et al., 2003
Neuropathy $H_{VDN}$

**Increased vulvar nerve density**
(Tympanidis et al., 2003)

**Increased CGRP-IR**
(Calcitonin Gene-Related Peptide)
(Bohm-Starke et al., 1999)

**Increased TRPV1-IR**
(Transient receptor potential vanilloid receptor, subtype 1)
(Tympanidis et al., 2004)
Central reorganization $H_{VDN}$

- Parahippocampal gyrus
- Basal ganglia

Schweinhardt et al. 2008
Sexual medicine: When good isn't good enough: treatment for vulvodynia

Nguyen, 2012 in Nat Rev Urology
Vulvodynia Mouse Model

Repeated Vulvovaginal Fungal Infections Cause Persistent Pain in a Mouse Model of Vulvodynia

Farmer et al., Science Transl Med (2011)

Aim 1. Test hypothesis that recurrent yeast infections can cause chronic vulvar hypersensitivity

Aim 2. Test hypothesis that prolonged inflammation can cause chronic vulvar hypersensitivity

Aim 3. Test hypothesis that repeated inflammation can cause chronic vulvar sensitivity
Study Design

Baseline
Von Frey
-Vulva
-Hindpaw

C. albicans
Inoculation
(10 x 5^4 cells/mL)

Days
-7
-3
0
4
11

Behavior

Infection

Resolution
32

Post-Infection
Von Frey
-Vulva
-Hindpaw

Daily Oral
Fluconazole
(15-50 mg/kg)
or
Saline
Study Design

**Infection Round #1**
- Baseline Von Frey -Vulva -Hindpaw
- C. albicans Inoculation (10 x 5^4 cells/mL)
- Behavior
- Infection
- Resolution
- Daily Oral Fluconazole (15-50 mg/kg) or Saline

**Infection Round #2**
- Post-Infection Von Frey -Vulva -Hindpaw
- C. albicans Inoculation (10 x 5^4 cells/mL)
- Behavior
- Infection
- Resolution
- Daily Oral Fluconazole (15-50 mg/kg) or Saline

**Infection Round #3**
- Post-Infection Von Frey -Vulva -Hindpaw
- C. albicans Inoculation (10 x 5^4 cells/mL)
- Behavior
- Infection
- Resolution
- Daily Oral Fluconazole (15-50 mg/kg) or Saline
Repeated vulvovaginal candidiasis produces persistent vulvar hypersensitivity

- **Candida + FLU**: 40% Allodynic*
- **Saline + FLU**: 5.5% Allodynic

*p = 0.02
Fisher’s Exact Test (one tailed)

Repeated Candida infection causes altered vulvar innervation

Zymosan (10 mg/mL) induces 4 hr vulvar pain

100% show mechanical sensitivity post-injection
7 day vulvar pain

- Mouse # 1
- Mouse # 2
- Mouse # 3
- Mouse # 4
- Mouse # 5
- Mouse # 6

Withdrawal Threshold (g)

Days

80% recover

20% persisting pain
3 wks vulvar pain

Withdrawal Threshold (g) vs Days

- Mouse # 1
- Mouse # 2
- Mouse # 3
- Mouse # 4
- Mouse # 5
- Mouse # 6

50% recover

40% persisting pain
7 wks vulvar pain

- Mouse # 1
- Mouse # 2
- Mouse # 3
- Mouse # 4
- Mouse # 5
- Mouse # 6

Withdrawal Threshold (g)

Days

- 50% recover
- 50% persisting pain
11 wks vulvar pain

Withdrawal Threshold (g)

Days

40% recover
Mice vary in the number of zymosan exposures required to produce persistent allodynia.


# Injections until Chronic Vulvar Allodynia
Conclusions

• VDN mouse model supports Inflammatory $H_{VDN}$

• Etiological theories are based on the chronic phenotype

• Too little is known of central involvement

• Detailed clinical phenotyping is needed

• Spinning our wheels: assessments must evolve
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Adaptive Immune Response

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Altered Innervation
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Estrogens

Nerve Growth Factors

Acute Inflammation