Chronic pelvic pain: mastcells, medical and psychological comorbidity

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DISCLOSURE

• Speakers’ bureau:
  Bayer, Biotest, Epitech, Janssen-Cilag, Pantarhei, Sanofi, Valeas

• Advisory Boards:
  Bayer, Janssen-Cilag, Novonordisk, Theramex, Valeas

• Consultant:
  Bayer, Epitech, Theramex
Question 1.
Chronic Pelvic Pain

What is the new evidence on the common biological correlates of chronic pelvic pain and inflammation?
Classification of Pain

PAIN

NEUROGENIC
("NOCICEPTIVE")

NEUROPATHIC

SUPERFICIAL

DEEP

SOMATIC

VISCERAL

PERIPHERAL

CENTRAL

Bonica, 1993; Melzack & Wall, 2000;
Turk et Al, 2001; Behrman et Al, 2006; Bernardes et al, 2007
A. Graziottin, 2011
Pain perception in women
contributing factors

Biological factors
PAIN: severity of tissue damage
neurological, mucocutaneous, vascular, muscular, endocrine, immunitory

Contextual factors
• quality of family support
• socioeconomic level
• working conditions
• social acceptance or not
• meaning of pain

Psychological factors
• fear of pain and its meaning
• coping strategies
• psychosexual history
• body image


A. Graziottin, 2010
### Non-cyclical chronic pelvic pain: risk factors
- a meta analysis -

<table>
<thead>
<tr>
<th>Factor</th>
<th>No of trials</th>
<th>No of women</th>
<th>(Cases:Controls)</th>
<th>SMD (99% CI)</th>
<th>OR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic factors</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Length of education</td>
<td>1</td>
<td>25</td>
<td>30</td>
<td>0.60 (-0.09 to 1.30)</td>
<td>3.00 (0.85 to 10.63)</td>
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<tr>
<td>Employment***</td>
<td>4</td>
<td>163</td>
<td>158</td>
<td>-0.11 (-0.43 to 0.22)</td>
<td>0.83 (0.46 to 1.49)</td>
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<tr>
<td>Marriage</td>
<td>6</td>
<td>215</td>
<td>166</td>
<td>-0.25 (-0.56 to 0.05)</td>
<td>0.63 (0.36 to 1.09)</td>
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<tr>
<td><strong>Environmental factors</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Lifetime drug/alcohol abuse</td>
<td>1</td>
<td>25</td>
<td>30</td>
<td>0.84 (0.05 to 1.63)</td>
<td>4.61 (1.09 to 19.38)</td>
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<tr>
<td><strong>Obstetric/gynaecological factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menarche</td>
<td>1</td>
<td>106</td>
<td>96</td>
<td>-0.10 (-0.46 to 0.26)</td>
<td>0.83 (0.43 to 1.61)</td>
</tr>
<tr>
<td>Greater parity</td>
<td>3</td>
<td>151</td>
<td>161</td>
<td>0.20 (-0.15 to 0.55)</td>
<td>1.43 (0.76 to 2.70)</td>
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<tr>
<td>Induced abortion</td>
<td>1</td>
<td>106</td>
<td>92</td>
<td>-0.19 (-0.65 to 0.27)</td>
<td>0.71 (0.31 to 1.63)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>1</td>
<td>106</td>
<td>92</td>
<td>0.61 (0.13 to 1.08)</td>
<td>3.00 (1.27 to 7.09)</td>
</tr>
<tr>
<td>Infertility</td>
<td>1</td>
<td>106</td>
<td>92</td>
<td>0.30 (-0.30 to 0.90)</td>
<td>1.73 (0.58 to 5.10)</td>
</tr>
<tr>
<td>Length of menstrual cycle</td>
<td>1</td>
<td>106</td>
<td>92</td>
<td>0.08 (-0.29 to 0.44)</td>
<td>1.15 (0.59 to 2.23)</td>
</tr>
<tr>
<td>Duration of menstrual flow</td>
<td>1</td>
<td>106</td>
<td>96</td>
<td>0.63 (0.27 to 0.99)</td>
<td>3.12 (1.62 to 6.05)</td>
</tr>
<tr>
<td>Endometriosis**</td>
<td>3</td>
<td>338</td>
<td>200</td>
<td>0.36 (0.07 to 0.65)</td>
<td>1.93 (1.14 to 3.27)</td>
</tr>
<tr>
<td>Sterilisation</td>
<td>2</td>
<td>165</td>
<td>861</td>
<td>0.15 (-0.10 to 0.40)</td>
<td>1.32 (0.84 to 2.06)</td>
</tr>
<tr>
<td>Previous pelvic inflammatory disease</td>
<td>2</td>
<td>127</td>
<td>424</td>
<td>1.02 (0.54 to 1.50)</td>
<td>6.35 (2.66 to 15.16)</td>
</tr>
<tr>
<td>Pelvic varices</td>
<td>2</td>
<td>248</td>
<td>188</td>
<td>0.33 (-0.15 to 0.80)</td>
<td>1.81 (0.76 to 4.28)</td>
</tr>
<tr>
<td>Previous caesarean section</td>
<td>2</td>
<td>1116</td>
<td>1083</td>
<td>0.64 (0.36 to 0.92)</td>
<td>3.18 (1.91 to 5.30)</td>
</tr>
<tr>
<td>Pelvic adhesions/other pathology**</td>
<td>3</td>
<td>338</td>
<td>200</td>
<td>0.49 (0.15 to 0.84)</td>
<td>2.45 (1.30 to 4.61)</td>
</tr>
</tbody>
</table>

Pallavi Latthe et al, Factors predisposing women to chronic pelvic pain: systematic review
BMJ 332; 74-755, 2006
Non-cyclical chronic pelvic pain: risk factors - a meta analysis -

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<th>OR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbed pregnancy</td>
<td>1</td>
<td>32/25</td>
<td></td>
<td>0.95 (0.18 to 1.72)</td>
<td>5.58 (1.39 to 22.39)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>178/241</td>
<td></td>
<td>0.45 (0.19 to 0.72)</td>
<td>2.28 (1.41 to 3.70)</td>
</tr>
<tr>
<td>Depression</td>
<td>8</td>
<td>410/376</td>
<td></td>
<td>0.55 (0.34 to 0.76)</td>
<td>2.69 (1.86 to 3.88)</td>
</tr>
<tr>
<td>Extroversion</td>
<td>1</td>
<td>35/9</td>
<td></td>
<td>-0.15 (-1.11 to 0.81)</td>
<td>0.76 (0.13 to 4.36)</td>
</tr>
<tr>
<td>Hysteria**</td>
<td>2</td>
<td>182/76</td>
<td></td>
<td>0.87 (0.51 to 1.23)</td>
<td>4.83 (2.50 to 9.93)</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>1</td>
<td>35/9</td>
<td></td>
<td>0.77 (-0.20 to 1.73)</td>
<td>4.01 (0.70 to 22.99)</td>
</tr>
<tr>
<td>Paranoia</td>
<td>1</td>
<td>37/23</td>
<td></td>
<td>1.45 (0.77 to 2.13)</td>
<td>13.89 (4.02 to 48.02)</td>
</tr>
<tr>
<td>Borderline syndrome</td>
<td>1</td>
<td>106/36</td>
<td></td>
<td>0.61 (-0.11 to 1.33)</td>
<td>3.02 (0.82 to 11.03)</td>
</tr>
<tr>
<td>Current phobias</td>
<td>1</td>
<td>25/30</td>
<td></td>
<td>0.74 (-0.21 to 1.70)</td>
<td>3.86 (0.69 to 21.71)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>1</td>
<td>25/10</td>
<td></td>
<td>0.94 (-0.37 to 2.25)</td>
<td>5.47 (0.51 to 58.84)</td>
</tr>
<tr>
<td>Psychosomatic symptoms***</td>
<td>8</td>
<td>303/250</td>
<td></td>
<td>1.15 (0.90 to 1.39)</td>
<td>8.01 (5.16 to 12.44)</td>
</tr>
</tbody>
</table>

Pallavi Latthe et al, Factors predisposing women to chronic pelvic pain: systematic review
BMJ 332; 74-755, 2006
## Anxiety and depression

<table>
<thead>
<tr>
<th>Type of pain</th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhea</td>
<td>OR=2.77</td>
<td>OR=2.59 Non sensuality: OR=8.12</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>OR=3.23</td>
<td>OR=7.77</td>
</tr>
<tr>
<td>CPP</td>
<td>OR=2.28</td>
<td>OR=2.69 PTSD= OR 5.47 Psychosomatic=8.01</td>
</tr>
</tbody>
</table>

Pallavi Latthe et Al, Factors predisposing women to chronic pelvic pain: systematic review BMJ 332; 74-755, 2006

A.Graziottin, 2006
The protagonists of the Chronic Pelvic Pain scenario

Central Nervous System

Peripheral Nervous System

Endometriosis

Who is the director of the pain orchestra?
The mast-cell is the powerful protagonist behind the clinical scenario of inflammation and pain.

More than 45,000 papers (!) credit the mastcell to be the director of the chronic inflammation orchestra.

Picture: Courtesy of R. Della Valle
The up-regulated mast cell

Menstrual blood in the tissue

Chemical & physical noxae

Estrogens

Infections

Mechanical trauma

Intercourse!!!

Neurogenic stimulus & neurotrophic changes
x 52-58% enlargement of peripheral neurons
x 10 Proliferation of pain fibers

Agonist stimuli

NERVE GROWTH FACTOR (x 50!)
Dupont et Al, 2001

A.Graziottin, 2005
From inflammation to chronic pain

Acute inflammation → Nociceptive pain → Restitutio ad integrum

Persistence or recurrence of factors causing tissue damage and inflammation

Chronic tissue inflammation Up-regulated mastcells

Chronic pain

Neuropathic pain

Depression

A. Graziottin, 2010
The interaction between mast cells and nerve fibers is the biological prerequisite of the shift from acute to chronic neuropathic pain.
Molecular Basis of Neuroimmune Interaction in an In Vitro Coculture Approach

NAKANISHI and FURUNO. Cellular & Molecular Immunology 2008

Time-courses of Fluo-3 fluorescence intensity changes in RBLs and in SCG neurites. An arrow indicates the time point of bradykinin addition.

Nerve-induced mast cell activation. Differential interference contrast image and sequential Ca$^{2+}$ images after the addition of bradykinin (time = 0) in the SCG-RBL coculture.
Molecular Basis of Neuroimmune Interaction in an *In Vitro* Coculture Approach

NAKANISHI and FURUNO. *Cellular & Molecular Immunology* 2008

**Mast cell-induced neurite activation.** Representative DIC image and sequential Ca2+ images after the addition of antigen (time = 0) in the SCG-RBL coculture. Arrowheads indicate the neurite which is strongly activated.

**Time-courses** of Fluo-3 fluorescence intensity changes in RBLs and in SCG neurites. An arrow indicates the time point of antigen addition.
**CENTRAL SENSITIZATION**

**CHRONIC MAST-CELL UP-REGULATION**

**FIRST NEURON**

**SECOND NEURON**

**ACTIVATED MICROGLIA**

**CROSS-TALK**

**NERVE LESION**

**Chronic Neuropathic Pelvic Pain - CPP**

A. Graziottin, 2011

Pathway from Inflammation to Depression

NEUROPLASTICITY

Depression

Neuroprotective microglia

Activated microglia

Blood-brain barrier

PSYCHOGENIC STIMULI

SPINAL-CORD NEUROINFLAMMATION

Conclusion 1

• The mast-cell is the director of the inflammatory process

• There is a close dialogue between mastcells and pain fibers

• They are intimately connected and use a common language: neurotransmitters and cytokines in the tissue and in the spinal cord/brain
Question 2.

Chronic Pelvic Pain and mastcells

What is the evidence on the key role of Mastcells in chronic pelvic pain syndromes?
Chronic Pelvic Pain: Medical & sexual comorbidities

- Endometriosis
  - deep dyspareunia
  - dysmenorrhea
  - infertility

- Pelvic inflammatory disease
  - infertility
  - deep dyspareunia

- Vulvar vestibulitis
  - introital dyspareunia
  - vulvodynia
  - post-coital cystitis

- Interstitial cystitis
  - bladder pain, dysuria
  - introital dyspareunia

- Irritable bowel syndrome
  - abdominal pain
  - dyspareunia

www.fondazionegraziottin.org
Heterogeneity of CPP.

Predictors of CPP include different factors:
- Biological: endometriosis, PID, CS, pelvic adhesions
- Affective: anxiety, depression, PTSD, Psychosomatic
- Context dependent: sexual and emotional abuse

Comorbidity is frequent and underdiagnosed

What is the common denominator of chronic pelvic pain?

CHRONIC INFLAMMATION Mediated by the MAST-CELLS and hyperactivation of pain fibers

A. Graziottin, 2011
Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis

**Objective:** To detect and quantify mast cells in peritoneal, ovarian, and deep infiltrating endometriosis and to study the relationship between mast cells and nerves in endometriosis.

**Tryptase-Positive Mast Cells Count**

<table>
<thead>
<tr>
<th>Tryptase + mast cells count.</th>
<th>Peritoneum</th>
<th>Ovary</th>
<th>Rectovaginal septum and Douglas pouch</th>
<th>Uterosacral ligament</th>
<th>Large bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>C</td>
<td>E</td>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Mast cells</td>
<td>7</td>
<td>4</td>
<td>5.6</td>
<td>0</td>
<td>10.8</td>
</tr>
<tr>
<td>SD</td>
<td>3.7</td>
<td>2.9</td>
<td>1.8</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: C = controls; E = endometriosis; NS = not significant. P values obtained after Bonferroni’s correction.</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis

Anaf et al; Fertil Steril 2006

Number of degranulating Mast Cells/mm²

<table>
<thead>
<tr>
<th></th>
<th>Peritoneum</th>
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<th>Rectovaginal septum and Douglas pouch</th>
<th>Uterosacral ligament</th>
<th>Large bowel</th>
</tr>
</thead>
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<td>E</td>
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<td>C</td>
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<tr>
<td>N</td>
<td>15</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Mast cells</td>
<td>3.3</td>
<td>1.5</td>
<td>7.5</td>
<td>0</td>
<td>8.1</td>
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<tr>
<td>SD</td>
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<td>&lt;.01</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: C = controls; E = endometriosis. P values obtained after Bonferroni’s correction.

Mast Cells Located < 25 µm from Nerve Structures

<table>
<thead>
<tr>
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<th>Rectovaginal septum and Douglas pouch</th>
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<tr>
<td>N</td>
<td>15</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Mast cells</td>
<td>0.33</td>
<td>0</td>
<td>0.33</td>
<td>4.13</td>
<td>6.8</td>
</tr>
<tr>
<td>SD</td>
<td>0.2</td>
<td>0</td>
<td>0.1</td>
<td>2</td>
<td>4</td>
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<tr>
<td>P</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Note: C = controls; E = endometriosis. P values obtained after Bonferroni’s correction.

Rich innervation of deep infiltrating endometriosis

There were significantly more nerve fibres in DIE (67.6+65.1/mm²) than in peritoneal endometriotic lesions (16.3+10.0/mm²) (P < 0.01).

DIE was innervated abundantly by sensory Aγ, sensory C, cholinergic and adrenergic nerve fibres; NGF, Trk-A and p75 were strongly expressed in endometriotic glands and stroma of DIE.

**CONCLUSIONS:** The rich innervation of DIE may help to explain why patients with this type of lesion have severe pelvic pain.
Mastcells in endometriosis
Conclusions

The presence of increased activated and degranulating mast cells in deeply infiltrating endometriosis and the close histological relationship between mast cells and nerves strongly suggest that mast cells could contribute to the development of pain and hyperalgesia in endometriosis, possibly by a direct effect on nerve structures.
Mastcells and Vulvar Vestibulitis

The chronically damaged introital tissue activates the up-regulation of the:

• mastcells, with increased production of pain factors and NGF
• nervous/pain system leading to vestibulitis/vulvodynia
• muscular system, with defensive contraction of the levator ani and myalgia


A. Graziottin, 2010
Symptoms: Dyspareunia and postcoital cystitis

Signs: vulvar vestibulitis and hyperactive pelvic floor
**Increase of Mastcells in the Vestibular mucosa**

- Increased concentration of mastcells higher (p<0.001) in the superficial layers vs the deep (0.05) (Bornstein et al, 2001, 2004, 2008)

**Normal mucosa**

**Mucosa in VVS**

Mast-cell produce NGF with proliferation of the free pain nerve terminals = increase of nociceptors X 10 times (Bohme-Starke et al, 2001, Bornstein, 2004)

Graziottin & Vincenti, 2004
Mastcells and vestibulilitis/vulvodynia
Conclusion 1.

Heparanase, which is degranulated from mast cells, is capable of degrading the vestibular stroma and epithelial basement membrane, thus permitting stromal proliferation and intraepithelial extension of nerve fibers. The hyperinnervation has been thought to cause the vestibular hyperesthesia distinctive of localized vulvodynia

Bornstein et Al, 2008
Mastcells and irritable bowel syndrome

The colon is the most important immunitary organ of human body

Colonic mastcells permanently control the mucosal boundary and “set the level” of the general immunitary, inflammatory and pain response

Hyperactivated colonic mastcells increase pain vulnerability in colon AND different organs, in the abdomen/pelvis such as bladder, vestibulum, and distant, ie brain

Food allergies increase pain vulnerability in different pain syndromes, such as endometriosis

Stanghellini et Al, 2006, 2008; Barbara et Al, 2004; Abar et Al, 2008
Activated Mast Cells in Proximity to Colonic Nerves Correlate With Abdominal Pain in Irritable Bowel Syndrome

Conclusions: Colonic mast cell infiltration and mediator release in proximity to mucosal innervation may contribute to abdominal pain perception in IBS patients.

Barbara et al; Gastroenterology 2004
Mastcells in the bladder pain syndrome BPS/IC ("interstitial cystitis")

Recurrent bladder inflammation leads to:

- Hyperactivation of mastcells in the bladder wall with chronic detrusorial inflammation and progressive scarring
- Increased production of pain signals
- Proliferation of pain fibers
- Defensive contraction of the levator ani

A.Graziottin, 2010
CONCLUSIONS

We recommend taking biopsies from the detrusor of patients with suspected BPS and examining them with tryptase-stained 3 μm thick sections, with every seventh section used for quantification; 27 mast cells/mm² is considered indicative of mastocytosis.
Question 3.
Endometriosis & Chronic Pelvic Pain

What bridges endometriosis, chronic inflammation and pain to depression?
Somatic Symptoms of Depression

• “Unexplained” pain
  – CPP, Backache, Chest pain, Chronic join pain, Limb pain, Headache, Bodily aches and Fibromyalgia
• Fatigue/loss of energy
• Insomnia
• Gastrointestinal symptoms
  – Abdominal cramping, bloating, heartburn, diarrhea and/or constipation
• Change in sexual desire & Female Sexual Disorders
• Weight loss or gain
  – Loss or increase in of appetite
• Dizziness & Palpitations

Major **brain** changes in depression

- Down-regulation of the
  - serotoninergic system:
    - § in the brain
    - § in the body (95% of serotonin is outside the brain!)
  - dopaminergic system
    1) seeking-appetitive-lust system
    2) motor system (nigro-striatal)
    3) logic linear thinking
  - opiatergic system

and **increase of inflammatory mediators**

A. Graziottin, 2010
NEW READINGS OF DEPRESSION

• as a systemic disease

as an inflammatory condition

with significant increase of inflammatory molecules produced by the mast cells.

Rakel RE. Depression. Prim Care 1999;26(2):211-224,
Trivedi MH. The link between depression and physical symptoms. Prim Care Companion J Clin Psychiatry 2004;6(Suppl 1):12-16,
Graziottin & Serafini, Menop.Int, 2009;
Inflammatory markers in depression

- **Major depression** is associated with a **proinflammatory response**, as indexed by elevation in C-reactive protein and cytokines such as **interleukin 6 and tumor necrosis factor-alpha**.

- Most studies support a **link** between **depression, inflammation and cardiovascular events**.

- **Antidepressants suppress the inflammatory response**. Whether or not the immune system is an appropriate target for antidepressant development has yet to be established.

Deception is an inflammatory state that may increase the risk of cardiac disease.

Inflammation & depression

Inflammation

Pain

Depression is (also) a systemic inflammatory state

Estrogens - and testosterone! - have an anti-inflammatory activity in the brain

Halbreich et al, 2001; Begliuomini et al, 2007; Brann Al, 2007; Dheen et Al, 2007; Foy et al, 2007; Hajszan et al, 2008; Raz et Al, 2008; Vegeto et Al, 2008; Dinan, 2009
Conclusion 3.

Depression:

- is a systemic disease
- is an inflammatory condition
- "somatizations" are the biological correlates of a systemic inflammatory state and of the widespread diffusion on neurotransmitters
The protagonists of the Chronic Pain scenario

Chronic inflammation

Peripheral Nervous System
PAIN FIBERS

Central Nervous System
PAIN CENTERS

Mast cell

Depression

Peripheral Nervous System
PAIN FIBERS

The Mast cell is the director of pain & depression orchestra
“Immunologic abnormalities, especially indices of excess inflammation, are a common finding in patients with depression.

There is increasing evidence suggesting that inflammation could, in a subgroup of patients and in some medical conditions contribute to the pathogenesis of depression.”

By Leah McNally, Zubin Bhagwagar and Jonas Hannestad in *Inflammation, Glutamate, and Glia in Depression: A Literature Review* 2008 CNS Spectr.13(6):501-509
Conclusion

CPP and comorbidities, such as Endometriosis, Vulvodynia, Bladder Pain Syndrome and IBS, are characterized by Mastcell mediated:

• inflammation
• depression
• pain
New perspectives

Down-regulation of the hyperactive mastcells / microglia is the new frontier

- in endometriosis & chronic inflammation
- in chronic pelvic pain

and in depression associated to chronic diseases

Immunological review
June 2007 vol 217 pag 5-337

Ren & Dubner, Nature medicine, October 14, 2010

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thanks for your attention
www.alessandragraziottin.it