Is There a Chronic Pain Prone Phenotype?

Yes, But its Often Much More Than Pain

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Pain Prone Phenotype

The Same Features:

- Are the seminal features seen in individuals with “central” pain states such as fibromyalgia
- Can identify the individuals within a cohort of “mixed” pain states that have “centralized”
- Are baseline features of individuals in the population that are at risk of subsequent development of pain
- Predict who will progress from acute to chronic pain
- Predict who will develop new post-surgical pain
  - Might also predict individuals who are unlikely to respond to a procedure
Evolution from Chronic Pain
“Prone” to Chronic Pain

Pain Prone Phenotype

- Female
- Early life trauma
- Family history of chronic pain
- Personal history of chronic centrally-mediated symptoms (multifocal pain with neuropathic descriptors, fatigue, sleep disturbances, psychological distress, memory difficulties)
- Cognitions such as catastrophizing
- Diffuse hyperalgesia, attenuated descending analgesia
- Functional neuroimaging

Exposure to “stressors” or acute, peripheral nociceptive input

New or different region of chronic pain
# Mechanistic Characterization of Pain

<table>
<thead>
<tr>
<th>Peripheral damage or inflammation</th>
<th>Neuropathic</th>
<th>Central pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily due to inflammation or mechanical damage in periphery</td>
<td>Damage to or entrapment of peripheral nerves</td>
<td>Augmented CNS pain processing (i.e. diffuse hyperalgesia)</td>
</tr>
<tr>
<td>May be relatively NSAID, opioid responsive</td>
<td>May responds to both peripheral and centrally acting analgesics</td>
<td>Primarily respond to drugs that alter levels of CNS neurotransmitters</td>
</tr>
<tr>
<td>Responds to procedures that correct underlying “problem”</td>
<td>Responds to surgery to relieve nerve compression (if present)</td>
<td>Surgery ineffective</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Classic examples</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Acute pain</td>
<td>Neuropathic low back pain</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>DPNP</td>
<td>IBS</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>PHN</td>
<td>TMJD</td>
</tr>
<tr>
<td>Cancer pain</td>
<td></td>
<td>Interstitial cystitis</td>
</tr>
</tbody>
</table>
Related Symptoms and Syndromes

- Tension/migraine headache
- Psychiatric comorbidities
- TMJD syndrome

Constitutional symptoms and syndromes
- Fatigue
- Sleep disturbances
- Idiopathic LBP

Functional GI disorders including IBS
- Nondermatomal paresthesias

- Memory and cognitive difficulties
- Dry and irritated eyes, rhinitis, tinnitus

- Multiple chemical sensitivity, “allergic” symptoms
- Esophageal dysmotility

- Neurally mediated hypotension, mitral valve prolapse
- Noncardiac chest pain

- Interstitial cystitis, chronic prostatitis, vulvodynia

It’s everywhere we look . . .

- **Interstitial cystitis/chronic prostatitis** – Multidisciplinary Approach to Chronic Pelvic Pain (MAPP) translational pain network
- **Post-deployment syndromes including mild TBI**
- **Osteoarthritis** – Phillips (Rheumatology), Hallstrom/Urquhart (Orthopedics), Murphy (PMR)
- **Low back pain** – Geisser (PMR)
- **Chronic pelvic pain, endometriosis** – As-Sanie (Ob/Gyn)
- **Temporomandibular joint disorder** – Gerstner (Dental School)
- **Perioperative setting** – Brummett (Anesthesiology)
- **Rheumatoid arthritis** – Lee (Brigham and Women’s)
- **Cancer pain** – Henry (Oncology), Smith (Nursing), Zick (CAM)
- **Vulvodynia** – Reed (Family Medicine)
- **“Irritative Eye Syndrome”** – Schtein (Ophthalmology)
Clinical Characteristics of Central Pain Conditions — I

- Typically characterized by:
  - Multifocal pain (use pain diagram)
  - Neuropathic descriptors of pain
  - Higher current and lifetime history of pain
  - Multiple other somatic symptoms (fatigue, sleep disturbances, mood disturbances, memory difficulties)

- Not “yes” or “no” — occurs over a wide continuum
  - Diagnostic labels (eg, FM, IBS, TMJD) largely historical and irrelevant\(^1\)
  - Wolfe et al. has shown that degree of “fibromyalgia-ness” predicts pain intensity, symptoms, and disability over a wide range of rheumatic disorders (RA, OA, regional musculoskeletal pain, FM).\(^2\)

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Clinical Characteristics of Central Pain Conditions — II

- 1.5 to 2x more common in females
- Strong familial/genetic underpinnings\(^1\)
  - Take family history of pain
- Triggered or exacerbated by stressors\(^2\)
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs\(^3\)

Familial/Genetic Predisposition to FM and Other Central Pain

- Familial predisposition shown for nearly any of these syndromes, but arguably best study in fibromyalgia\(^1\)
- Most recent work by Arnold, et al suggests >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders
- Kato et. al. have performed a series of twin studies suggesting approximately 50% of risk is genetic and 50% environmental

Genes that may be involved in fibromyalgia
- Serotonin (5-HT2A receptor polymorphism\(^2\), transporter\(^3\))
- Dopamine (D4 receptor exon III repeat polymorphism\(^4\))
- COMT (catecholamine o-methyl transferase)\(^5\)

“Stressors” Capable of Triggering These Illnesses\textsuperscript{1,2}

- Early life stressors\textsuperscript{3}
- Peripheral nociceptive input from rheumatic disease (e.g. osteoarthritis, RA, SLE) or acute injury\textsuperscript{4}
- Physical trauma (automobile accidents)\textsuperscript{5}
- Certain catastrophic events (war but not most natural disasters)\textsuperscript{6}
- Infections\textsuperscript{7}
- Psychological stress/distress

Role of Infections in Triggering Pain

*It’s Not Just Herpes Zoster*

- Infections can trigger regional or widespread pain in approximately 10% of exposed individuals
  - *The initial location of the infection determines the subsequent pain syndrome*
  - Common upper respiratory infections are not capable of triggering these conditions

- Infections causing diffuse pain and fatigue (e.g., EBV, Lyme disease, brucellosis, Ross River virus, Q Fever) lead to fibromyalgia and/or CFS in 7 – 10% of cases

- Any type of infectious diarrhea will trigger IBS in 10 - 20% of those exposed¹

- Interstitial cystitis, chronic prostatitis, and vulvodynia are all often preceded by infections in those regions of the body²

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Role of Infections in Triggering These Illnesses

Dubbo study

- Network of 92 MDs in Dubbo region of Australia performed population-based longitudinal study of serologically confirmed new cases of acute Epstein-Barr virus, Q fever, or Ross River virus
- There were dramatically different rates of these infections, and they had differing acute presentations, but 9% of each type (22/250 total) met criteria for persistence fatigue and somatic sx. at 12 months
- Four factors of post-infective or chronic fatigue state were very similar despite initial infection, and included fatigue, pain, mood disturbance, and “neurocognitive” factors
- The only predictor of the likelihood of developing CFS was the intensity of the original somatic symptoms. Was not associated with:
  - Cytokine profile of acute infection
  - Clearance of pathogen
  - Baseline psychological factors

Childhood Factors Predictive of Adult Chronic Widespread Pain (CWP)

- Best data are from the 1958 British Birth Cohort Study (individuals born within a single week in UK in 1958)
  - Data on many symptoms including abdominal pain and headache, collected on 10,453 7 year old children, by maternal self-report
  - Similar data collected on these same children as 11 and 16 years old
  - Individuals then surveyed by mail at age 45, and 7,470 participants returned survey (71%)
  - Study has the advantage of not relying on retrospective self-report
1958 British Cohort Study

- The presence of pain, or multiple symptoms in childhood was associated with subsequent development of CWP (OR 1.5)\(^1\)

- Children hospitalized following motor traffic accident (OR 1.5), who resided in institutional care (OR 1.7), who experienced a maternal death (OR 2.0), and familial financial hardship (1.6) were more likely to have CWP as adults.

- These associations were not explained by adult psychological distress or social class.

Role of Psychological Distress in Triggering These Illnesses

- Baseline psychological distress is only weakly associated with the subsequent development of CWP (OR 1.5 – 2)\(^1,2\)
- Higher rates seen in many case-control studies because they were performed in tertiary care settings, and/or considered "somatization" or illness behaviors as "distress"

- Studies immediately pre- and post-the US 9/11 attacks failed to note any increase in pain or related symptoms
- No increase in somatic symptoms amongst individuals in the general population living in NYC\(^3\)
- No increase in pain or fatigue levels in fibromyalgia patients followed from prior to the attacks to one month afterwards in Washington DC\(^4\)

Treating Peripheral Pain Generators May Reduce Hyperalgesia and Central Sensitization - I

- Female patients with FM and either (a) myofascial pain (n=68) or (b) concurrent OA (n=56).

- Patients were randomized to receive (a) myofascial trigger point injection vs. sham needling, or (b) steroid ionophoresis to affected joint or sham ionophoresis.

- Evaluations were repeated on days 4 and 8 of both overall pain and tenderness.

Treating Peripheral Pain Generators May Reduce Hyperalgesia and Central Sensitization - II

- After therapy, in active – but not placebo-treated groups: number and intensity of myofascial/joint episodes and paracetamol consumption decreased and pressure thresholds at trigger/joint increased (p < 0.001); FM pain intensity decreased and all thresholds increased progressively in tender points and the non-painful site (p < 0.0001).

- At a 3-week follow-up, FM pain was still lower than basis in patients not undergoing further therapy and had decreased in those undergoing active therapy from day 8.

Many neurotransmitters influence CNS pain processing and other co-morbid symptoms

**Facilitation**
- Substance P
- Glutamate and EAA
- Serotonin (5HT$_{2a, 3a}$)
- Nerve growth factor

**Inhibition**
- Descending anti-nociceptive pathways
- Norepinephrine-serotonin (5HT$_{1a,b}$), dopamine
- Opioids
- GABA
- Cannabianoids
Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms

- Increased distress
- Decreased activity
- Isolation
- Poor sleep
- Maladaptive illness behaviors

Dually Focused Treatment

- Pharmacological therapies to improve symptoms
- Nonpharmacological therapies to address dysfunction

CNS Contributions to Pain

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Summary

- There is a ubiquitous cluster of pain and other somatic symptoms such as fatigue, insomnia, distress, and memory difficulties that may represent one of the most common and vexing “diseases” in man.

- This entity can occur in isolation (e.g. fibromyalgia, irritable bowel syndrome) or co-morbid with peripheral/nociceptive pain states.

- Current evidence suggests that approximately 50% of the risk of developing this symptom complex is genetic and 50% environmental.
Summary

- This syndrome is often triggered or exacerbated by a variety of “stressors,” and goes by many different names that are historical and/or related to the “pathogenic biases” (often peripherally-based) of the medical sub-specialty seeing these individuals.

- The most plausible explanation for these syndromes is that abnormalities in both “trait” and “state” levels of CNS neurotransmitters that control pain processing as well as level of alertness, sleep, mood, and memory.

- We’ve been looking for pain in all the wrong places.
  - The brain is complicated . . . but is the most important organ in pain.