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

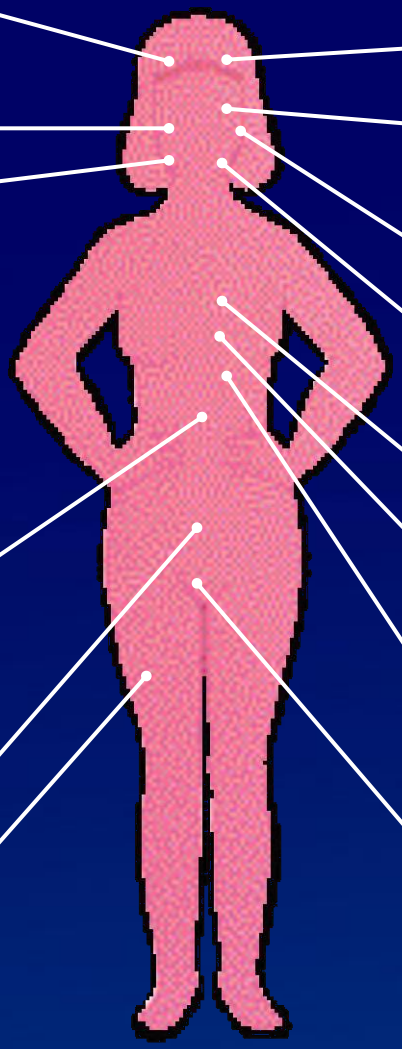
New or different region of chronic pain

Mechanistic Characterization of Pain

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

▪ **Classic examples**
  ▪ Acute pain
  ▪ Osteoarthritis
  ▪ Rheumatoid arthritis
  ▪ Cancer pain
	▪ **Classic examples**
	  ▪ Neuropathic low back pain
	  ▪ DPNP
	  ▪ PHN
		▪ **Classic examples**
		  ▪ Fibromyalgia
		  ▪ IBS
		  ▪ TMJD
		  ▪ Interstitial cystitis

Related Symptoms and Syndromes



Tension/migraine headache

Psychiatric co-morbidities

TMJD syndrome

<u>Constitutional symptoms and syndromes</u>

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

Aaron LA, et al. *Arch Intern Med.* 2000;160:221-227. Williams & Clauw *J Pain.* 2009;10(8):777-791.

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]

1. Ablin K, Clauw DJ. *Rheum Dis Clin North Am.* 2009;35:233-251. 2. Wolfe F, Michaud K. *J Rheumatol.* 2006;33:1516-1522.

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]

1. Kato K, et al. *Psychol Med.* 2008;39:497-505. 2. Ablin K, Clauw DJ. *Rheum Dis Clin North Am.* 2009; 35:233-251. 3. Watson NF, et al. *Arthritis Rheum*. 2009;60:2839-2844.

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]

1. Arnold et al. *Arthritis Rheum*. 2004;50:944-52. 2. Bondy et al. *Neurobiol Dis*. 1999;6:433-9.
3. Offenbaecher et al. *Arthritis Rheum*. 1999;42:2482-8. 4. Buskila et al. *Mol Psychiatry*. 2004;9:730-1.
5. Gürsoy et al. *Rheumatol Int*. 2003;23:104-7.

"Stressors" Capable of Triggering These Illnesses[1,2]

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

1. Clauw D, et al. *Neuroimmunomodulation*. 1997;4:134-153. 2. McLean SA, et al. *Med Hypotheses.* 2004;63:653-658. 3. Jones et. al. 2007 ACR meeting. 4. Clauw et. al. JCR 1997. 5. McBeth 2006 ACR meeting. 6. Clauw et. al. J Occup Environ Med. 2003 Oct;45(10):1040-8. 7. Ablin et. al Sem Arthritis Rheum 2009.

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 exposed[1]
- Interstitial cystitis, chronic prostatitis, and vulvodynia are all often preceded by infections in those regions of the body[2]

1. Parry et. al. Am J Gastroenterol. 2003 Sep;98(9):1970-5. 2. Warren et. al. Urology. 2008 Jun;71(6):1085-90

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[2]
- Baseline psychological factors

1. Hickie et. al. *BMJ.* 2006 September 16; 333(7568): 575. 2. Cameron et. al. 575 Infect Dis 2006;193: 664-71.

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

1. Jones GT, et.al. Arthritis Rheum 2007:56(5):1669-75. 2. Jones GT, et.al. Pain 2009:143:92-96.

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]

1. Croft et. al., Annals of the Rheumatic Diseases 1996; 55(7):482-485. 2. Papageorgiou et. al. Ann Rheum Dis 2002; 61(12):1071-1074. 3. Raphael et. al. Pain 2002:100:131-8. 4. Williams JAMA, 2003:289(13):1637-8.

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.

G. Affaitati et al. / European Journal of Pain 2010; in press.

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 ($p < 0.0001$).

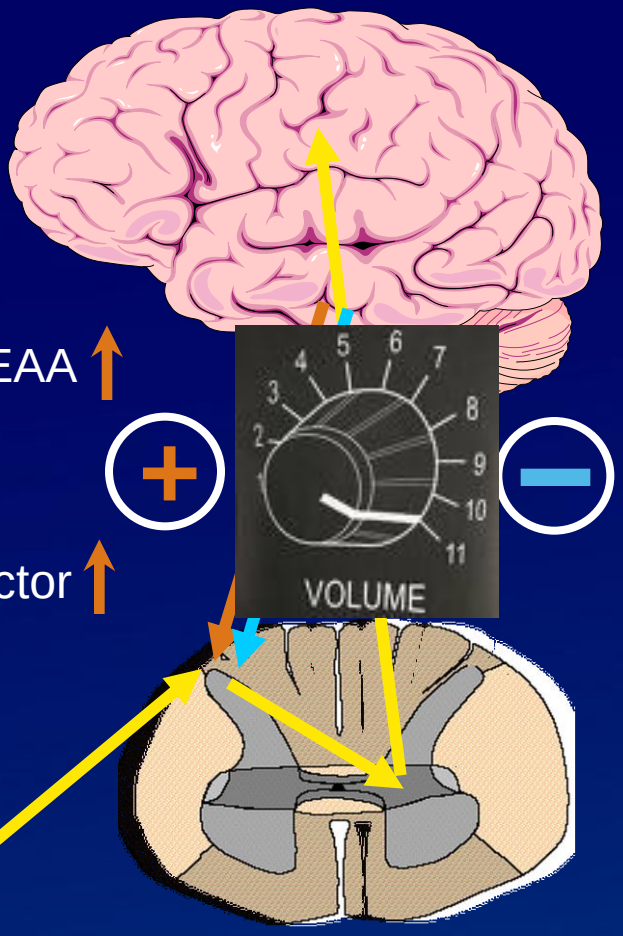
- At a 3-week follow-up, FM pain was still lower than basis in patients not undergoing further therapy and had decreased in those undergoing active therapy from day 8.

G. Affaitati et al. / European Journal of Pain 2010; in press.

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
- Cannabanoids

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**

Clauw and Crofford. *Best Pract Res Clin Rheumatol*. 2003;17:685-701.

CNS Contributions to Pain

Pain Prone Phenotype

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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