

FIBROMYALGIA

Pathogenesis, Diagnosis and Therapeutic Options

Kevin V. Hackshaw, MD
Associate Professor of Internal Medicine
and Molecular Biochemistry
Fellowship Director, Rheumatology
Division of Rheumatology & Immunology
The Ohio State University Wexner Medical Center

No Financial Disclosures

- 1 - Case Presentation
- 2 - History of Fibromyalgia/ Contrast with Chronic Fatigue Syndrome = Systemic Exertion Intolerance Disorder
- 3 - Pathogenesis of Fibromyalgia and Neuropathic Pain
- 4 - Clinical Presentation and Diagnosis
- 5 - Other Considerations and corollary conditions
- 6 - Therapeutic Options and Closing Tips

Case Presentation

- 33 year old Female
- History of Migraines
- History of Irritable Bowel Syndrome
- Diffuse total body pain
- “feels like I’ve been run over by a truck”

- Has exceeded her FMLA allotment of days off
- Concentration difficulties at work
- Job performance has declined
- “I fear I’m going to be fired”

Physical Examination

- Height 5’4” Weight 178
- HEENT: Malar erythema (flushed)
- Extremities: Hands/ feet cool to touch
- Neurological: Control points negative with painful tender points elicited in 18/18 sites. Moderate hyperalgesia. No muscle atrophy. Give way muscle weakness in proximal and distal muscles

Laboratories

- Comprehensive Metabolic Profile: Normal
- CBC: Normal
- ANA: 1:160, diffuse; ENA battery: Negative
- ESR: 22
- Vitamin D: 22 (nl 30 – 100)
- TSH: 1.8
- Diagnosis

FIBROMYALGIA

- A chronic musculoskeletal pain amplification syndrome
- Fatigue
- Wide spread muscular aching
- Sleep disturbance
- Temperature intolerance

A MAJOR CAUSE OF DISABILITY AND MORBIDITY

- 25.3% OF PATIENTS RECEIVED DISABILITY PAYMENTS; (Wolfe, 1996)
- 27.8% OF PATIENTS WERE SEEKING/RECEIVING DISABILITY; (Robinson, 2007; J Pain)
- 31% OF PATIENTS EMPLOYED PRIOR TO ONSET OF THEIR FM REPORTED LOSS OF EMPLOYMENT DUE TO THEIR DISEASE (Thorson, 1998)

Associated conditions

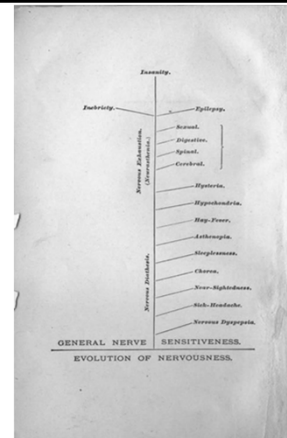
- Neuralgia
- **Neurasthenia**
- Muscular Rheumatism
- Psychogenic Rheumatism
- Tension Rheumatism
- Fibrositis/ Myofibrositis
- **Chronic Fatigue Syndrome**
- Shell Shock
- Post Traumatic Stress Syndrome
- Gulf War Syndrome
- Chemical Hypersensitivity Syndrome
- Sick Building Syndrome



George M. Beard

George Miller Beard (1839-1883)

Associated neurasthenia with the stresses of urbanization and the increasingly competitive business environment. People were attempting to achieve more than their constitution could cope with (Wikipedia)



American Nervousness, Its Causes and Consequences (1881) - Author: George Miller Beard

- **Chronic Fatigue Syndrome (CFS = SEID)**
- **Systemic Exertion Intolerance Disease**
- Clinical case definition: symptoms should be present for at least six months and have moderate, substantial, or severe intensity at least one-half of the time. Other criteria include: post-exertional malaise, sleep problems, cognitive impairment, and orthostatic-related symptoms.
- Other names: Myalgic Encephalomyelitis (UK) , Chronic fatigue and immune dysfunction syndrome

Demographics for Fibromyalgia

- Female > Male (5:1) *
- Age Onset: 9 – 60
- Most commonly between 40 and 60
- All Races
- Between 3 – 7% of the U.S. population is affected
- Inciting events:
Trauma (**), Infection, MVA with whiplash, Head or Neck Injury

Pain Mechanisms

“PAIN”

An unpleasant sensory and emotional experience associated with actual or potential tissue damage

PAIN MECHANISMS

- *Nociceptive transmission: arising from inflammation or degeneration of joints and soft tissue*
- *Examples: Rheumatoid Arthritis and Osteoarthritis*

PAIN MECHANISMS

- *Neuropathic transmission: arising from a primary lesion in the peripheral or central nervous system*
- *Hyperresponsiveness to subthreshold stimuli*
- *Examples: Trigeminal Neuralgia, Diabetic Peripheral Neuropathy, Post herpetic neuralgia, Fibromyalgia*
- *Nociceptive*
- *Inflammatory*
- *Neuropathic*
- *Maladaptive*

PERIPHERAL AND SPINAL PAIN MECHANISMS

- **NOCICEPTIVE AFFERENTS**
 - A delta myelinated (fast transmission)
 - C unmyelinated (slow transmission)

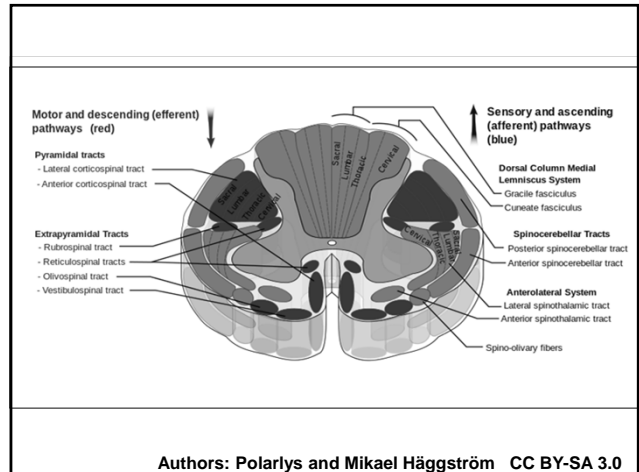
PERIPHERAL AND SPINAL PAIN MECHANISMS

- **CENTRAL ENDINGS** -spinal cord gray matter
- **MODULATING FACTORS** {5HT – High presynaptic levels inhibit NT release, low levels enhance NT release}
- **NEUROTRANSMITTERS**
 - substance P (NK1 receptors; long acting)
 - glutamate (NMDA receptors; short acting)
 - Excitatory Amino Acids
 - vasoactive intestinal peptide (visceral organs)
 - CGRP

DESCENDING CONTROLS

• MODULATION OF NOCICEPTIVE PROCESSING AND PAIN

- perceptual correlates
 - placebo effect
 - hypnosis and suggestion
 - combat, athletics
 - ritual analgesia
 - pharmacological analgesia



Mechanisms of Neuropathic Pain

- Spontaneous discharges either peripherally or centrally
- Localized demyelination, DRG abnormalities or aberrant Sodium or Calcium channels may contribute
- Aberrant expression of neurotransmitters in periphery or centrally leads to “Sensitization”
- Results in more ectopic firing

Clinical Presentation of Fibromyalgia

- **ALLODYNIA**
A NON-NOXIOUS
STIMULUS ELICITS
PAIN
- **HYPERALGESIA**
AN EXAGERRATED
RESPONSE TO A
PAINFUL STIMULUS

Fibromyalgia Spectrum

- **Seek Medical Care**
- **Multiple tender points**
- **Depression ***
- **Anxiety ***
- **High frequency of recent stressful experiences**
- **Don't seek medical care**
- **Multiple tender points**

Rheumatic symptoms

- **General aches/ pains**
- **Articular pains without joint swelling**
- **Morning stiffness about 1 hour**
- **Subjective morning swelling**

Non-rheumatic symptoms

- **Anxiety**
- **Sleep disturbances**
- **Headaches**
- **Irritable bowel syndrome**
- **Irritable bladder**
- **PMS**
- **Numbness**
- **Palpitations**
- **Mottled skin appearance**
- **Temperature instability**

FIBROMYALGIA TENDER POINTS



National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Diagnostic Criteria - 1990

- Widespread subjective aching for more than 3 months
- Pain in >11 of 18 tender points
- Subjective stiffness of more than 3 months
- Pain in all 4 quadrants of body
- “Normal Labs” to include ESR, TSH, ANA*, Vitamin D Level (?), etc.
- Concurrent chronic fatigue, emotional distress, poor sleep, morning stiffness *specific diagnostic criteria
- * +ANA may be seen in 30% of FM patients

2010 Preliminary Diagnostic Criteria

- Widespread Pain Index +
- Symptom Severity Scale
- WPI (measure of number of painful body regions – from list of 19 areas)
- SS score (estimated degree of fatigue, waking unrefreshed, cognitive symptoms; and number of somatic symptoms in general (Arth Care Res 2010: 62, 600.)

Preliminary Diagnostic Criteria

Muscle pain	Oral ulcers
Irritable Bowel	Heartburn
Numbness/Tingling	Fatigue/ Tiredness
Thinking difficulty	Seizures
Headache	Tinnitus
Abdominal cramps	Blurred vision
Dry mouth	Chest Pain
Itching	Hives
Shortness of breath	Raynauds
Raynauds	Dry eyes
Hives	Hearing difficulties
Chest Pain	Frequent urination
Rash	Nervousness
Fever	

Symptoms in patients with chronic fatigue syndrome - SEID

<u>Symptom</u>	<u>Percent of patients</u>
Easily fatigued	100
Difficulty concentrating	90
Headache	90
Sore throat	85

Symptom **Percent of patients**

Tender lymph nodes	80
Muscle aches	80
Joint aches	75
Feverishness	75
Difficulty sleeping	70
Psychiatric problems	65

***CLINICAL SIMILARITIES
BETWEEN FIBROMYALGIA
AND SEID (CFS)***

Associated common symptoms

80 to 90 percent women, usual age 20 to 55 years

Myalgias and fatigue > 90%

Neurocognitive and mood disturbances

Headaches

Sleep disturbances

No identifiable cause

Testing is normal

Physical examination usually normal except for tender points which are required for diagnosis of fibromyalgia and present in most patients with chronic fatigue

Normal laboratory and radiologic tests

Chronic symptoms, no highly effective therapy

Other Considerations...

Pain Catastrophizing

- Individuals who catastrophize have difficulty shifting their focus of attention away from painful or threatening stimuli
- Attach threat or harm to non-painful stimuli
- Describing pain as “awful, horrible or unbearable”

Waddell Signs

Tenderness

superficial - skin is tender to light pinch over a wide area of lumbar skin

nonanatomic - deep tenderness over a wide area, not localized to one structure

Simulation Tests - give the impression that an examination is being done, when in fact it is not

axial loading - vertical loading over the standing patient's skull by the examiner's hands

rotation - turn standing patient to one side by rotating lower extremities (not spine)

Waddell Signs

Distraction Tests –
reevaluating a positive finding while the patient's
attention is not focused on the test
indirect observation –

*Can patient move the body part without pain when
not being directly examined?
straight leg raise - if positive when examined
supine, do "flip test" (sitting SLR)*

*Regional Disturbances - widespread divergence from
accepted neuroanatomy
weakness - "cogwheeling" or many muscle groups
that cannot be explained neuroanatomically
sensory - "stocking" distribution of sensory changes*

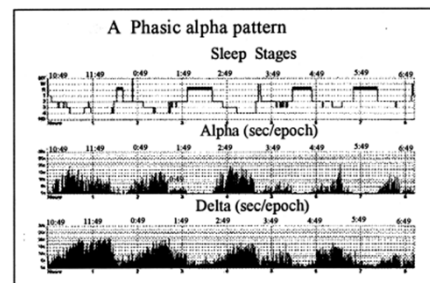
*Overreaction
disproportionate verbalization, facial expression, muscle
tension and tremor, collapsing, sweating*

Comorbidity

- 25% of RA with FM
- 30% of SLE with FM
- 50% of Sjogrens Syndrome with FM
- 20 -80% of DM with FM
- 50% Multiple Sclerosis with FM

Pathogenesis

PHASIC ALPHA WAVE INTRUSION PATTERNS CORRELATE WITH CLINICAL SYMPTOMS IN FIBROMYALGIA

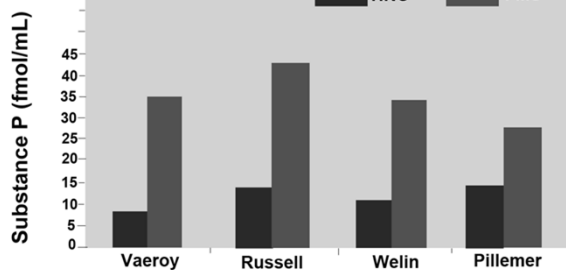


Roizenblatt, S., Moldofsky, H., Benedito-Silva, A. A. and Tufik, S. (2001). Alpha sleep characteristics in fibromyalgia. *Arthritis & Rheumatism*, 44: 222-230. doi: 10.1002/1529-0131(200101)44:1<222::AID-ANR29>3.0.CO;2-K

Family and Genetic Studies

- Odds ratio for a family member of a patient with FM to also have FM is 8.5 (Arnold, 2004)
- FM family members have increased pain sensitivity as measured by total myalgic score

Genetic influences on pain sensitivity may in part mediate the relation between somatization and the development of widespread pain



Substance P in CSF

- No significant relationship with depression (Russell, 1994)
- No difference in CSF SP levels between individuals with major depression and normal controls (Deuschle, 2005)
- CSF SP levels are unchanged by antidepressant treatment / response (Deuschle, 2005)

NGF, BDNF and Glutamate in CSF of FM

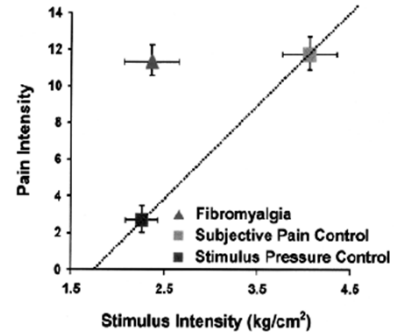
Table - CSF Levels of NGF and BDNF (Mean +/- 2 SD) in Patient Groups and Controls

	CM PATIENTS		PFMS		CONTROLS	
NGF (pg/mL)	46.7	4.6	47.2	5.3	13.7	2.7
BDNF (pg/mL)	39.4	6.7	40.4	4.6	11.3	3.4
Glutamate (mol/L)	2.18	0.4	2.36	0.3	1.37	0.3

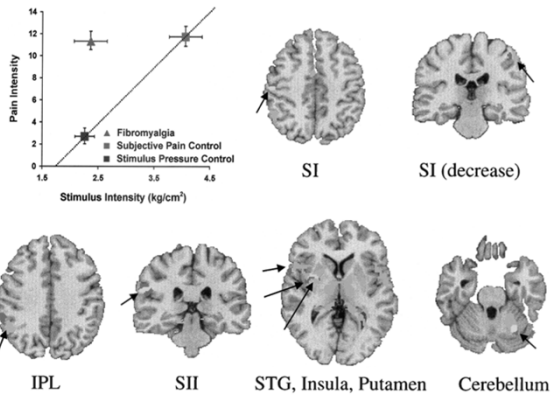
Abbreviations: CM, chronic migraine; PFMS, primary fibromyalgia syndrome; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor. * = Statistically Significant

Sarchielli et al., 2007

FM PATIENTS REPORT PAIN AT NORMALLY PAINLESS PRESSURES

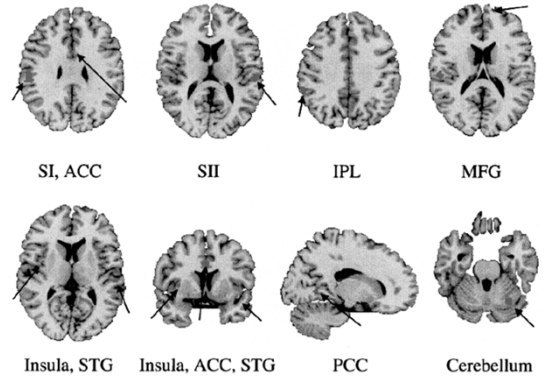


Gracely, R. H., Petzke, F., Wolf, J. M. and Clauw, D. J. (2002), Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis & Rheumatism*, 46: 1333-1343. doi: 10.1002/art.10225



Gracely, R. H., Petzke, F., Wolf, J. M. and Clauw, D. J. (2002), Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis & Rheumatism*, 46: 1333-1343. doi: 10.1002/art.10225

NORMALLY PAINLESS PRESSURES ACTIVATE FM BRAINS UNIQUELY



Gracely, R. H., Petzke, F., Wolf, J. M. and Clauw, D. J. (2002), Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis & Rheumatism*, 46: 1333-1343. doi: 10.1002/art.10225

Treatment

Treatment Options

(after exercise program has been established *)

- *Medication Class*
- 1-Tricyclic Antidepressants
- 2-Analgesics
- 3-SNRI's *
- 4-SSRI's
- 5-Anticonvulsants (A2D) *
- 6-Other anticonvulsants (Na channel)
- * FDA approved
- *Study Results*
- 1-8 and 12 week trials: Some +, Most -
- 2-All - except tramadol
- 3-All +
- 4-All -
- 5-All +
- 6-Most have not been tested
- * FDA approved

Treatment Regimens

- Pregabalin 50 qhs x 1 wk
- 50 bid wk 2
- 50/100 wk 3; etc.
- Milnacipran 12.5 mg day 1
- 12.5 mg bid days 2 and 3
- 25 bid days 4 - 7
- 50 bid thereafter
- Gabapentin 100 or 300 mg po qhs
- Titrate up q 2 weeks
- Eventually bid or tid; etc.
- Tricyclics 10 mg po qhs
- Titrate up by 10 q month, etc.
- Duloxetine 30 mg qAM wk 1
- 60 qAM thereafter
- Treat symptom domains for most patients; ie., sleep, fatigue, pain, etc.

Other Treatment Considerations

- Cognitive Behavioral Therapy
- Local Trigger Point Injections
- Topical Capsaicin
- Stimulants
- Muscle Relaxants / Anti inflammatories
- NMDA Antagonists (Dextromethorphan)

Treatment of CFS/SEID

**Cognitive Behavioral Therapy
Graded Exercise Therapy**

**Both have been beneficial
Adaptive pacing therapy has not
proven to be beneficial**

Cognitive Behavioral Therapy

CBT is effective either in individual, group or internet based
A series of one-hour sessions designed to alter beliefs and behaviors that might delay recovery

A form of treatment that focuses on examining the relationships between thoughts, feelings and behaviors. By exploring patterns of thinking that lead to self-destructive actions and the beliefs that direct these thoughts, people with mental illness can modify their patterns of thinking to improve coping. CBT is a type of psychotherapy

Graded Exercise Therapy

A strategy for graded exercise therapy includes establishment of a baseline of achievable patient-specific exercise or physical activity, followed by an incremental increase in the duration of time spent physically active. A target heart rate range should be set to avoid overexertion, generally <100 beats per minute. Ultimate goal of 30 minutes of light exercise five times a week. When this goal is achieved, the intensity and aerobic nature of the exercise can be gradually increased. Any titratable sustainable activity is appropriate, including walking, swimming, and the use of exercise machines, and activities can be mixed. Graded exercise therapy should be supervised by a physical therapist or exercise therapist.

Other treatments

Similar treatment paradigm as used with Fibromyalgia

TCA's, etc.

SSRI's have a much greater role

AVOID:

immune serum globulin, rituximab, acyclovir, galantamine, fluoxetine and other antidepressants, methylphenidate and modafinil (stimulants), glucocorticoids, amantadine, doxycycline, magnesium, evening primrose oil, vitamin B12, Ampligen, essential fatty acids, bovine or porcine liver extract, dialyzable leukocyte extract, cimetidine, ranitidine, interferons, exclusion diets, BioBran MGN-3 (a natural killer cell stimulant), and removal of dental fillings.

Laboratories

- Comprehensive Metabolic Profile: Normal
- CBC: Normal
- ANA: 1:160, diffuse; ENA battery: Negative
- ESR: 22
- Vitamin D: 22 (nl 30 – 100)
- TSH: 1.8
- Diagnosis

SUMMARY

- The pathogenesis of FM has more in common with neuropathic pain spectrum disorders than the typical inflammatory or degenerative musculoskeletal pain disorders
- Treatments should be directed towards CNS mechanisms
- FM and classical neuropathic pain syndromes respond similarly to drugs of several different chemical classes with different MOA consistent with shared pathogenic mechanisms