

Western Occupational and Environmental Medical Association
CME Webinar - August 18, 2011

Fibromyalgia

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PLEASE STAND BY - WEBINAR WILL BEGIN AT 12:00pm (Pacific Time)
For Audio: Call: 866-740-1260 / Access Code: 764 4915#

Disclosures

None

Question 1

How would you best describe Fibromyalgia?

- 1. A connective tissue disease?
- 2. A psychiatric disease?
- 3. A CNS disease?
- 4. A disease in the patient's head?

Question 2

Which of the following is true in FM patients?

- 1. See higher levels of TNF and IL8?
- 2. See accelerated grey matter loss?
- 3. First degree relatives have a 8 fold higher risk?
- 4. Poor delta wave sleep?

Common Misperceptions

1. Fibromyalgia is in the patient's head and is not a real entity.

- Difficult because FM has no single etiology
- Subjective complaints
- Normal PE findings
- Normal bloodwork

Functional Neuroimaging

■ Allows one to visualize how the brain processes the sensory experience of pain

■ Several modalities

functional MRI

MR Spectroscopy

SPECT

PET

Functional Neuroimaging

- Proton Magnetic Resonance Spectroscopy
- Noninvasive method of assessing in vivo neuronal tissue by assessing brain metabolites
- N-acetyl aspartate (NAA) is a marker of neuronal integrity and function
- See low NAA levels in the hippocampus
- Hippocampus inhibits stress response

Functional Neuroimaging

- Positron Emission Tomography
- Dopamine is an important neurotransmitter for pain inhibitory pathways
- One study described altered dopaminergic activity that was diminished when compared to controls

Functional Neuroimaging

- SPECT imaging in multiple studies find reduced cerebral blood flow to the right thalamus, an area of the brain important in the modulation of pain response
- On brain MRI in FM see premature aging of the brain with accelerated gray matter loss
- 3 times greater age associated decrease in grey matter than in healthy controls

Diffuse Noxious Inhibitory Control

- Intrinsic analgesic system
- System activated after an acute painful stimulus
- Goal to decrease the pain intensity by activating endogenous endorphins
- In fibromyalgia see diminished responsiveness of this system

Serologic and Biochemical Abnl

- FM patients have higher antiserotonin ab, antiganglioside ab, antiphospholipid ab when compared to controls in many studies
- No statistical difference in presence of ANA, antithyroid antibodies
- Substance P neuropeptide released from axons
- Substance P levels increased in blood/CSF
- Proinflammatory cytokines TNF alpha and Interleukin 8 levels are increased, and they decrease with treatment

Neurohormonal Abnormalities

- Abnormal HPA axis seen in several studies
- Hyperactivity of the stress response
- Flattened diurnal cortisol level
- Elevated cortisol trough

Autonomic Dysfunction

- Higher resting heart rates
- Decreased heart rate variability
- Abnormal drop in BP during tilt table testing
- Increased findings of orthostatic hypotension

Genetics

- Increasing evidence supports a genetic predisposition
- First degree relatives have an 8 fold higher risk of developing the syndrome
- Polymorphisms in serotonin receptor, dopamine 4 receptor and catecholamine o-methyl transferase enzyme have been described
- These polymorphisms effect compounds that have a critical role in sensory processing of pain

Sleep Abnormalities

- Stage 1-2: non REM, light sleep, _ waves
- Stage 3-4: REM, deep sleep, delta waves
- In FM alpha wave sleep cycles predominate
- FM patients have poor delta wave sleep w/ alpha wave intrusion
- High rate of Obstructive Sleep Apnea

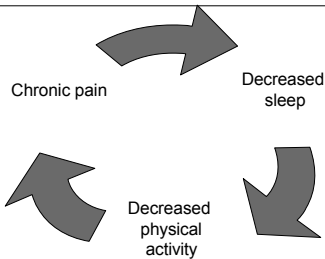
Is Fibromyalgia real???

- Abnl on functional imaging of brain
- Abnl in the Hypothalamic-pituitary axis
- Autoantibodies to neurotransmitters involved in analgesia
- Diminished CNS descending inhibitory control
- Genetic susceptibility with polymorphisms in genes encoding neurotransmitters
- Elevated neuropeptides
- Autonomic reactivity

Is Fibromyalgia real???

- There is accumulating data suggesting **disordered central pain processing**
- Unclear if represent the cause or the effect of the disease, but there clearly are objective findings
- Prototype of a chronic pain syndrome
- Not a true connective tissue disease

Pathophysiology



Epidemiology of Fibromyalgia

- Affects 8:1 female:male
- Average age 30-55
- Prevalence in US is >2%
- Prevalence increases with age: 8% at age 70
- Second most common rheumatologic diagnosis

Symptoms

- Diffuse muscle and joint pain
- Fatigue present in over 90%
- Non-restful sleep in greater than 70%
- Depression, anxiety
- Headaches, mental fog, decreased short-term memory
- Subjective swelling in joints and muscles
- Raynaud's occurs in 10%
- Neurologic symptoms: numbness, tingling, burning
- **Up to 50% of patients notice symptoms begin after a specific event**

Diagnostic Criteria

- 1990 ACR classification criteria
- Compared 293 FM and 265 control patients with OA, RA, and low back pain, arm and neck pain
 - Controls selected to be those usually difficult to distinguish from fibromyalgia
 - Over 300 variables (history, exam, lab, radiographic) were analyzed

Physical Examination

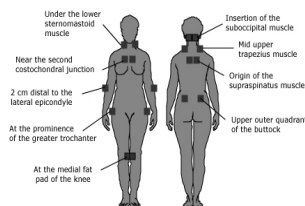
- Key is excessive tenderness to palpation of soft tissues
- Tender points are specific regions that are more sensitive to applied pressure
- These regions are exceedingly tender in FM patients compared to control patients

Classification Criteria

- Recommended diagnostic criteria:
 1. widespread musculoskeletal pain
 2. symptoms for greater than 3 months
 3. presence of 11/18 positive tender points should be both above/below waist, and bilateral
- Sensitivity 80%, specificity 80%
- Used in clinical trials
- Simple to use in clinical practice

Physical Examination

- 4kg/cm pressure
- Enough to blanch thumbnail



Problems with 1990 Criteria

- Tender point exam was not being done in primary care, where most FM dx made
- FM diagnosis in primary care is often a symptom based diagnosis
- The 1990 criteria did not incorporate with myriad of symptoms patients have

New 2010 Preliminary Criteria

- Wolfe et al published new criteria
- Preliminary, not yet replaced 1990 criteria
- Have done away with tender point exam
- It is completely subjective, based upon patient's symptoms
- Can be assessed using a questionnaire

Widespread Pain Index (WPI)

- Asks patient to note the number of areas that he has had pain in over past week
- There are 19 areas listed
- Score 0-19
- Shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw, chest, abdomen, neck, upper back, lower back

Symptom Severity Scale (SS)

- Fatigue
- Waking unrefreshed
- Cognitive symptoms

- On a scale of 0-3, patient indicates how severe each symptom has been in past week

ACR 2010 Preliminary Criteria

- A patient has FM if the following 3 are met:
- 1. Widespread pain index ≥ 7 and symptom severity score ≥ 5 OR widespread pain index 3-6 and SS ≥ 9
- Symptoms present for 3 months or more
- Exclusion of other disorders

ACR 2010 Preliminary Criteria

- These are still being evaluated
- They have not yet replaced the 1990 criteria
- They need to be studied in primary care
- They need to be evaluated in patients with other rheumatic disorders

Physical Examination

- How to differentiate FM from true arthritis?
 - Absence of true effusions of joints
 - Absence of joint deformity
 - Absence of warmth over joints
 - Normal range of motion of joint

Question 3

You have a new patient with FM, what do you order?

- 1. ANA and ANA subsets?
- 2. TSH?
- 3. HIV and Hepatitis panel?
- 4. ESR and CRP?

Additional Testing

- Important to do a thorough musculoskeletal and neurological examination
- Laboratory tests unremarkable
- Done to exclude other underlying diseases
- Radiologic studies unnecessary

Common masqueraders

- Hypothyroidism
- PMR
- Rheumatoid Arthritis
- SLE
- Chronic viral infections
- Inflammatory myositis
- TSH
- ESR, CRP
- RF, anti-CCP
- ANA
- Hepatitis, HIV, EBV
- CK, AST, ALT

Common Misperceptions

2. Fibromyalgia is a psychiatric disease.
- There is an increased incidence of anxiety, depression in patients
 - 25% of pt with FM have current depression
 - Lifetime prevalence of anxiety disorder is 64%, depression is 75%
 - Little evidence for somatization disorder or malingering

Physical Trauma

- Buskila 1997: FM 13X more frequent after neck injury than after lower extremity fracture
- Tishler 2006: No increase in FM frequency after whiplash injury (prospective)
- Buskila 2009: 15% of Israeli train crash survivors develop FM over 3 years

Workers Seeking Disability

- Study with 103 patients with repetitive strain injury
- Suffering pain above and below the diaphragm, far more than the arm pain for which they were referred
- 73 met the ACR Criteria for Fibromyalgia
- Indistinguishable from 165 patients with FM that was not work-related
- Their illness is far more global

- Helfenstein and Feldman 2000

Chronic Disabling Occupational Musculoskeletal Disorders

- 449 patients presenting with CDOMD
- 68% met criteria for fibromyalgia (9% prior dx)
- Most had more than one injured body part
- 2 times more likely to be female
- 4.4 times more likely with dx cervical injury
- 5.6 times less likely to return to work

- Howard et al 2002

Common Misperceptions

3. Little can be done to treat Fibromyalgia.
- There are many treatments available
 - No one gold standard therapy
 - Multidisciplinary approach is key

Importance of Treatment

- FM has substantial compromise on:
 - Quality of life
 - Impairment of function
 - Short-term disability
 - Higher work absenteeism
 - Higher direct and indirect healthcare costs

Treatment of Fibromyalgia

1. Education, education, education!!!
 - Many feel rejected by the medical profession "It is in their head"
 - Fear that a life-threatening illness will eventually be found

Assurance that is it a real syndrome
Relationship of neurohormones to pain perception
No disfigurement or increased mortality
There are treatment options
Symptom improvement takes time
Majority of patients live normal and active lives

Patient Education

- Has a therapeutic effect
- In studies with educational component to treatment, patients had significantly more improvement than controls
- Beneficial effects lasted 3-12 months after sessions lasted

Treatment

2. Aerobic Exercise

- Best validated treatment to date
- Improves mm conditioning, restorative sleep, increases endogenous endorphins in the CNS
- Reassure patient that exercise safe to do
- Start slowly, and titrate up
- Low impact aerobics: walking, biking, swimming
- Swimming is an excellent option
- Goal is daily aerobic exercise, 30-45 minutes

Treatment

3. Physical Therapy

- To help structure an exercise program
- Massage
- Local heat
- TENS

Treatment

4. Medical therapy

- Tricyclic antidepressants
- Cyclobenzaprine (Flexeril)
- SSRIs
- Neurontin
- Lyrica
- Cymbalta
- Analgesia with Tylenol, Tramadol, Opioids

Question 4

Which of the therapies have long-term benefit in patients with Fibromyalgia?

- 1. Gabapentin?
- 2. Elavil?
- 3. Tramadol?
- 4. Cymbalta?

Anti-inflammatories

- NSAIDs often used by patients
- NSAIDs alone no better than placebo
- NSAIDs may have synergistic effect when combined with CNS active medications
- Prednisone at 20mg a day was ineffective

Tricyclic Antidepressants

- Amitriptylene and nortriptylene
- First drugs to be intensively studied in FM
- Increase synaptic [] of serotonin and norepinephrine in the CNS by inhibiting reuptake
- Benefit within first two weeks of therapy
- Helps with pain, sleep and fatigue
- Anticholinergic SE increase with dose
- Nortriptylene has a better SE profile
- Short-term efficacy well described
- Studies have not shown prolonged beneficial effect past 8-12 weeks

Cyclobenzaprine

- Shares tricyclic structure with TCA
- Centrally acting skeletal muscle relaxant
- Studies show benefit in pain and sleep
- Short-term use <12 weeks
- Dose is 10-40mg a day
- Long-term studies show no advantage over placebo

SSRIs

- Increases serotonin at neuronal synapse
- May be just as effective as TCA
- Strongest data with Fluoxetine (Prozac), followed by Paroxetine (Paxil)
- With other SSRIs data is limited, lacking or inconclusive
- Combination of SSRIs and TCA more effective than either alone- Prozac in AM, Elavil in PM

Serotonin-Norepi Reuptake Inhibitors

- Duloxetine (Cymbalta)- tablets 20mg, 30mg, 60mg
- Cymbalta second FDA approved medicine
- Cymbalta dose is 60mg daily to bid
- Superior to placebo in trials < 12 weeks, short-term efficacy
- 120mg dose associated with more AE and no more beneficial
- Start at 30mg for one week, may then increase to 60mg
- Common AE: somnolence (up to 15%), dizziness (up to 14%), nausea (up to 22%), transaminitis (1%), antiplatelet effect, many drug interactions
- Do not use with hepatic insufficiency
- Need dose adjustment if GFR <30
- Need gradual discontinuation

Savella (Milancipram)

- Approved January 15, 2009
- 3rd FDA approved medicine for Fibromyalgia
- Showed to be superior to placebo up to 29 weeks
- Tablets come in 12.5mg, 25mg, 50mg, 100mg
- Recommended dose is 100mg/day
- Titrate up to 50mg bid over one week
- No dose adjustment with hepatic impairment
- Need adjustment if GFR < 30
- Most common AE is nausea, constipation, hot flush, hyperhidrosis
- No weight gain associated with it

Pregabalin (Lyrica)

- First FDA approved medicine June 2007
- Disrupts neuronal signaling by binding to alpha 2 delta subunit of Ca channels in CNS
- Doses: 150mg to 450mg daily
- Adjust dose with renal impairment, dialyzable
- Decreases pain and fatigue, improves sleep
- Appears to maintain effect over 6 months
- AE common and dose related- dizziness (49.2%), somnolence (28%), peripheral edema (16%), weight gain (16%)

Gabapentin (Neurontin)

- Frequently prescribed for chronic pain
- At 12 weeks, more effective than placebo
- Improved pain and sleep quality
- Doses used are often too low
- Titrate up to efficacy and SE profile
- Average 1800mg daily (up to 2400mg)
- Adjust with renal impairment, dialyzable
- AE: somnolence (20%), dizziness (28%), edema (8%)

Antiepileptics

- Topamax
- Tegretol

Treatment of Fibromyalgia

5. Pain control

- Tramadol is a centrally acting synthetic opioid that also weakly inhibits norepinephrine and serotonin reuptake
- Tramadol/Tylenol combination showed some improvement in clinical studies
- Vicodin and narcotics

Alternative Therapies

- Acupuncture
- Yoga
- Meditation
- EMG biofeedback
- Cognitive behavioral therapy
- Hypotherapy

Treatment Algorithm

1. Clinical suspicion of Fibromyalgia
2. Rule out secondary causes
Send ESR, CRP, RF, ANA, TSH
3. Patient education and reassurance
4. Exercise program/ Physical Therapy/
Accupuncture
5. Trial of Elavil 10-25mg qhs, titrate up
6. Addition of SSRI, Neurontin or Lyrica
7. Pain control

Prognosis

- No increase in mortality
- Not a deforming disorder
- Chronic disorder
- Significant impact in daily life, work, socialization, relationships
- Most patients do get some improvement
- Significant improvement in 25% patients
- Remission in 25%

Importance of Treatment

- Current treatment approaches attempt to influence central pain mechanisms
- Heterogeneity of patients makes “one-size-fits-all” approach less efficacious
- Therapeutic responses, although good, are not durable
- Successful treatment may require regular assessment and possible rotation of meds

Fibromyalgia

- Accumulating evidence supporting an amplified CNS response to pain
- Simple guidelines exist for diagnosis
- Important to rule out disease masqueraders
- There are many therapies that are available that help to balance the hyperactive CNS
- Multidisciplinary approach is key

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