FIBROMYALGIA
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COMMOM MISPERCEPTION #1
Fibromyalgia is in the patient’s head and is not a real entity.
• Unknown etiology
• Subjective complaints
• Normal PE findings
• Normal bloodwork

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, we see diminished responsiveness of this system

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
• FM patients have low NAA levels in the hippocampus – the front portion of the brain involved in regulating emotions and memory and inhibits stress response (1)
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

- In multiple studies, SPECT imaging found 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 patients, see premature aging of the brain with accelerated grey matter loss
- 3 times greater age associated decrease in grey matter than in healthy controls

SEROLOGIC AND BIOCHEMICAL ABNL

- FM patients have higher anti-serotonin ab, anti-ganglioside ab, anti-phospholipid ab when compared to controls in many studies
- No statistical difference in presence of ANA, anti-thyroid antibodies
- Substance P levels increased in blood/CSF
- Pro-inflammatory 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 affect compounds that have a critical role in sensory processing of pain
**SLEEP ABNORMALITIES**

- Stage 1-2: non REM, light sleep, a 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 presence of 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**

Chronic pain → Decreased sleep

Decreased physical activity → Decreased sleep

**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

**EPIDEMIOLOGY OF FIBROMYALGIA**

- Leads to approximately 5.5 million ambulatory visits/yr
- Average total annual cost estimate: $5945 per person
  - Office visits
  - ER visits
  - Procedures
  - Laboratory tests
  - Hospitalizations
**Symptoms**

- Fatigue in > 90%
- Sleep issues in > 70%
- Depression, anxiety
- HA, mental fog, memory issues
- Subjective swelling
- Neuro symptoms
- Up to 50% of patients notice symptoms began after a specific event

**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

**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 the myriad of symptoms patients have

**New Preliminary 2010 Diagnostic 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
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

- Do a thorough musculoskeletal and neurological 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

ADDITIONAL TESTING

- Lab are done to exclude other underlying diseases
- Radiologic studies unnecessary
- Sleep Study considered in those with large neck size, sleep disturbances, RLS, headaches, HTN
- EMG-NCV, muscle biopsy, MRI not indicated unless objective findings suggesting a disease other than FM

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

MISPERCEPTION #2: Fibromyalgia is a psychiatric disease.

- There is an increased incidence of anxiety, depression
- 25% of pts with FM have concomitant depression
- Lifetime prevalence of anxiety disorder is 64%, depression is 75%
- Little evidence for somatization disorder or malingering
COMMON Misperception #3

“Little can be done to treat Fibromyalgia”
• There are many treatments available
• No one gold standard therapy
• Multidisciplinary approach is key
  1. Non-pharmacologic
  2. Pharmacologic

MULTIMODAL TREATMENT APPROACH TO FIBROMYALGIA

| Cognitive behavioral therapy | Obtain info about disease and resources
|                            | Deal with negative thoughts
|                            | Recognize exacerbating or triggering factors
|                            | Participate in support groups

| Complementary / alternative therapies | Relieve stress (ie. Massage, acupuncture)
|                                        | Exercise (Best validated treatment to date)
|                                        | Physical therapy
| Lifestyle changes                     | Sleep hygiene
|                                        | Make changes at work [delegate, adopt]
|                                        | Eat well

THE IMPORTANCE OF EDUCATION

• Many feel rejected by the medical profession because of the stigma: “It is in their head”
• Fear that a life-threatening illness will eventually be found

Assurance that it is 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

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
• Physical therapy: TENS, massage, structure!

PHARMACOLOGIC TREATMENT

| FDA Approved for Fibromyalgia | Pregabalin (Lyrica, anticonvulsant) |
|                              | Duloxetine (Cymbalta – SNRI)       |
|                              | Milnacipran (Savella – SNRI)       |
| TCAs                         | Amitriptyline (Elavil - low dose)**|
| Antiseizure agents           | Gabapentin [Neurontin]             |
| Analgesics                   | Tramadol (Ultram)                 |
|                             | Acetaminophen/ NSAIDs – NOT effective|
| SSRIs/ other SNRIs           | Used to treat associated depression|
| Muscle relaxers              | Used to treat stiffness, spasms   |
| Sleep aids                   | Modafinil (Provigil) for fatigue  |
| For sleep disturbances       | Trazodone (Desyrel)               |
|                             | Ropinirole (Requip) for RLS       |
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%)

SEROTONIN-NOREPIREUPTAKE INHIBITORS

- Duloxetine (Cymbalta)—tablets 20mg, 30mg, 60mg
  - Cymbalta dose is 60 mg daily to bid
  - Superior to placebo
  - 120 mg 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%), antiparkinson effect, many drug interactions
  - Do not use with hepatic insufficiency
  - Need dose adjustment if GFR < 30
  - Need gradual discontinuation

- Milnacipran (Savella)—tablets 12.5 mg, 25 mg, 50 mg
  - Savella dose is 50 mg BID
  - Start at 12.5 mg for one week, then titrate weekly to max effective dose 50 mg BID
  - Some AEs
  - No dose adjustment with hepatic impairment
  - Need dose adjustment if GFR < 30
  - Need gradual discontinuation

TRICYCLIC ANTIDEPRESSANTS

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

GABAPENTIN (NEURONTIN)

- Frequently prescribed for chronic pain
- Less expensive substitute for pregabalin
- 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%)

TREATMENT ALGORITHM

1. Clinical suspicion of Fibromyalgia
2. Rule out secondary causes
   ---- Send ESR, CRP, RF, ANA, TSH, etc
3. Patient education and reassurance
4. Exercise program/Physical Therapy
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

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

SUMMARY

• 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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