온몸이 아파요! - 섬유근통의 진단과 치료

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Evolution from Chronic Pain
“Central” Pain Prone Phenotype
- Female
- Genetics
- Early life trauma
- Family history of chronic pain and mood disturbances
- Personal history of chronic centrally-mediated symptoms (multifocal pain with neuropathic descriptors, fatigue, sleep disturbances, psychological distress, memory difficulties)
- Cognitions such as catastrophizing
- Lower mechanical pain threshold and descending analgesic activity

“Stressors” Capable of Triggering These Illnesses
(Supported by Case-Control Studies1-4)
- Early life stressors3
  - Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5 – 2X more likely to have CWP 42 years later
- Peripheral pain syndromes (e.g. RA, SLE, osteoarthritis)4
- Physical trauma (automobile accidents)5
- Certain catastrophic events (war but not natural disasters)6
- Infections7
- Psychological stress/distress
  3. Jones et al. 2007 ACR meeting.

Exposure to “stressors” or acute, peripheral nociceptive input
Psychological and behavioral response to pain or stressor
New or different region of chronic pain

- 218 -
Genetics of Pain

Pain is known to be very genetic in that it strongly runs in families in humans, and differs within species of inbred rats and mice.

Several specific genes have been shown to play major roles in pain sensitivity thus far:

- α1,β1 channel is associated with insensitivity to pain, whereas mutations (1.8, 1.9) that lead to increased function leads to erythromelalgia or paroxysmal extreme pain disorder.
- GTP cyclohydrolase 1 (GCH1)
- Cathecol-O-methyltransferase (COMT)
- KCNS1
- P2X7 receptor

Neural Influences on Pain and Sensory Processing

Facilitation
- Substance P
- Glutamate and EAA
- Serotonin
- Nerve growth factor

Inhibition
- Dopamine
- Noradrenalin (NA, NE)
- GABA
- Cannabinoids

Pharmacological Therapies for Fibromyalgia (i.e. Central Pain)

- Dual reuptake inhibitors such as: tramadol
- New anticonvulsants (topiramate, gabapentin)
- Opioids
- Antidepressants
- Anticonvulsants

Mechanistic Characterization of Pain

Any combination may be present in a given individual

- In the presence of peripheral sensitization
- In the presence of central sensitization
- Mixed Pain States

Treatments for Pain Based on Underlying Mechanisms

<table>
<thead>
<tr>
<th>Peripheral Mechanism</th>
<th>Non-inflammatory</th>
<th>Inflammatory</th>
<th>Peripheral</th>
<th>Centralized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
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<tr>
<td>NSAIDs/acetaminophen</td>
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<tr>
<td>Immunosuppressants, Anti-inflammatories</td>
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<tr>
<td>Tricyclics SNRIs</td>
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<td>Alpha-2 delta ligand anticonvulsants</td>
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<tr>
<td>Tricyclics SNRIs</td>
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Injections, surgical procedures less effective or ineffective for individuals with centralized pain

References:
Evaluation of the Effectiveness of Pregabalin in Alleviating Pain Associated with Fibromyalgia: Using Functional Magnetic Resonance Imaging Study

Seong-Ho Kim1, Youngho Lee2, Sunggyun Lee2, Chi-Woong Moe2

Abstract

Purpose: To assess the efficacy of pregabalin by showing differences in the neuronal activities of fibromyalgia (FM) patients before and after longitudinal treatment using functional magnetic resonance imaging (fMRI).

Methods and Materials: In total, 21 female patients with FM and 11 age- and gender-matched healthy controls participated. FM patients underwent fMRI at baseline and following pharmacological therapy with pregabalin to diminish their pain. Pressure-pain stimuli were delivered on the subject’s thumb, and the hand during MRI scans. Brain activation regions in FM were evaluated for longitudinal changes using a paired t-test. Changes in clinical features were also assessed with the Fibromyalgia Impact Questionnaire (FIQ), Brief Fatigue Inventory (BFI), Beck Depression Inventory (BDI), Wide Range Pain Index (WRPI), Symptom Severity Scale Score (SSS), and State-Trait Anxiety Inventory (STAI).

Results: Clinical scores were reduced significantly following treatment with five of the six clinical tests (FIQ, BFI, BDI, WRPI, SSS; p < 0.05). Brain activation post-treatment was significantly lower than that pre-treatment in 13 regions of the brain (p < 0.01).

Conclusions: Our findings confirm that pregabalin influences aspects of the whole-pain matrix, using fMRI, inducing longitudinal changes in neuronal activity during the pain state, and that it reduces pain and other core symptoms of FM. This method could be applied to other longitudinal clinical trials of pharmacological treatments for FM.

Nonpharmacological Therapies

- Strong Evidence
  - Education
  - Aerobic exercise
  - Cognitive behavior therapy
- Modest Evidence
  - Strength training
  - Hypnotherapy, Biofeedback, pain therapy
- Weak Evidence
  - Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound
- No Evidence
  - Tender (trigger) point injections, flexibility exercise

Cognitive Behavioral Therapy for Chronic Pain

- Shown to be effective over a wide range of pain states
- Effect sizes on function (.4 -.6) are much greater than typically seen with pharmacological therapies
- Despite wide agreement that these help, barriers to implementation have been:
  - Physicians do not strongly recommend these therapies and there is no “industry” promoting these therapies
  - Not generally reimbursed by third parties
  - Not enough trained therapists to give one-on-one CBT to all chronic pain patients

Exercise to Treat Chronic Pain

- OA of knee
  - SMD of .49 for pain and .37 for physical function. Studies that involved direct supervision of 12 or more sessions somewhat more likely to lead to improvement.
- OA of the hip
  - Small improvement in pain but not function.
- Fibromyalgia
  - Aerobic exercise improves global well being (SMD .49), function (SMD .66) and pain (SMD .69 but very wide CIs include 0).
  - Strength training may also be effective although far fewer studies have been performed.


Neurostimulatory Therapies

Peripheral

- TENS
  - Conventional TENS (C-TENS) is given at high stimulation frequency with low intensity, and pain relief is almost immediate but short-lived.
  - Acupuncture like TENS (AL-TENS) is given at low frequency and high intensity (which is uncomfortable to many individuals), and generally has a longer lasting analgesic effect.
  - AL-TENS decreased pain and joint tenderness in RA
- Leads to improvements in both pain and function in OA.

Neurostimulatory Therapies

Central - Being shown to be effective across a broad range of chronic pain conditions

- Applied to scalp
  - Transcranial Magnetic Stimulation (TMS)
  - Direct Current Stimulation (DCS)
- Implantable
  - Spinal cord stimulation
  - Vagal nerve stimulation
  - Deep brain stimulation

Symptoms of Pain, Fatigue, etc.

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

Dually Focused Treatment

Functional Consequences of Symptoms

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

Subgroups of FM Patients

<table>
<thead>
<tr>
<th>Group 1 (n=50)</th>
<th>Psychological factors neutral</th>
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<tbody>
<tr>
<td>Tender</td>
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<tr>
<td>Not very tender</td>
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<tr>
<td>Low depression/anxiety</td>
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<tr>
<td>Moderate control over pain</td>
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<thead>
<tr>
<th>Group 2 (n=31)</th>
<th>Psychological factors worsening symptoms</th>
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</thead>
<tbody>
<tr>
<td>Tender</td>
<td></td>
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<tr>
<td>High depression/anxiety</td>
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<tr>
<td>Very high catastrophizing</td>
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<tr>
<td>No control over pain</td>
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<thead>
<tr>
<th>Group 3 (n=16)</th>
<th>Psychological factors improving symptoms</th>
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<tbody>
<tr>
<td>Extremely tender</td>
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<tr>
<td>Low depression/anxiety</td>
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<tr>
<td>Very low catastrophizing</td>
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<tr>
<td>High control over pain</td>
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1. Low levels of depression & anxiety, normal cognition, tenderness

40세 여자, 관절 가이드
3년 정도 지속되는 다발성 관절통 및 복, 어깨, 어깨, 다리 통증을 주소로 내원함

대부분의 관절에서 벗어난 모양 중상들은 스트레스나 주변의 날씨 등에 의해 약화되고, 운동 및 이완 활동에 의해 완화되는 경향

발열, 심장, 소화기 등에 영향을 미치며, 대략 1개월 동안 발생하였으며, 엄청난 스트레스와 신경계 및 면역계의 동반

관절 및 후방은 통증이 약화되고, 감각, 흡수증, 전반적인 불안

저구강, 잠의 저하, 제자리에 앉아 있는 재미, 혈착


2. High level of tenderness and depression

49세 여자, 10여년 된 전신성 통증을 주소로 내원함

10여년 전 교통사고 이후 복통이 나타나기 시작한다고 잠재적

최측 통증이 더 약화되었으며, 밤에 더 심해짐

초음파, 진단 검사 및 치료 모두 실패

통증이 심해짐과 함께, 고통, 자주 어려움, 우울

저구강, 약간의 구토, 비행

저항은 상당히 약하며, 감각, 하부의 통증은 약간

저구강, 잠의 저하, 저작, 심장

저구강, 잠의 저하, 저작, 심장

저구강, 잠의 저하, 저작, 심장

저구강, 잠의 저하, 저작, 심장
3. Tender, no negative psychological or cognitive factors

- 29세 여자, 컴퓨터 업무자, 7-8년 전 전신성 풍부를 주소로 내원함
- 이형계 풍부가 시작되었는지 잘 모르고 함
- 풍부의 약간 또는 완전 오해 없음
- 날에 따른 통증의 기복이 있음
- 피곤함 지속 존재하지만, 업무상 바쁘고 그렇지 않아서 잘 못하고 있음 (감각)
- 8시간 정도 지속하면 개인의 느낌 없음
- 최근에 풍부가 약화되었고, 남자 친구의 가벼운 풍부 정도에도 풍부는 느끼지 않음
- 외래성 건강이 보이며, 기본 및 인지 상태도 풍부

입원등 14/16 아와 특이 소견 없음

2010: 8+5

A. Secondary FM

#1. SLE (with Hx of autoimmune thrombocytopenia)
#2. Secondary FMS
#3. TMD (temporomandibular disorder)

42세 여자 5년 전부터 SLE로 진단된 화자로 내원 3개월 전부터 시작된 다발성 관절염을 주소로 내원함
- 전신적인 불편 및 피로, 수면장애, 두통, 움직임에 풍부가 없이 오랫동안 진행된 관절염 경과의
- 최근 전지 전부터 양손과 좌측 팔목과 팔꿈치 통증이 심해짐
- 어린 시절부터 잡종은 있으나 부족은 없었고, 입원일은 12/18
- 일부 혈액검사 검사 값은 감사 난간 후 기존의 tapersing 품의로 Pd를 5mg bid로 품을 12일 후에 다시 보고함
- 1주일 후 전신적인 통증과 어린 환자들은 오래 이어 약화되었으며, Pd 품장 후 어지러움 및 의사결정에 심해짐. 검사실 소견은 모두 정상
- NS, AMT, AMT, Cyclobenzaprine, SNRI 품에 효과가 없고 유해반응만 나타남

B. Chronic localized pain FM

32세 남자, 6개월 지속된 우측 풍부 통증을 주소로 내원함
- 목근육 질병발생 및 대량발생에서 심장내과 및 풍부외과 정형외과 치료의
- 학생 및 풍부를 시행하였으나 모두 약효가 없었음
- 여러 진단을 체크한 결과 목혈액에도 반응이 없어 전원됨
- 풍부의 기복이 있으나 환자시 사라지지 않으다고 함
- 병력정리상 최근 5개월간의 약을 없었으며, 전신에 걸친 통증도 함께 발생함
- 수면공급 및 피로감도 호소함

우측 4.5 복부부위의 풍부 및 입원등 11/18
- 본원 심장내과 및 풍부관절 및 전신 콜드전 등의 검사에서도 특이 소견 없음

Learning points

- good prognosis
- significant functional impairment - encourage to exercise
- cognitive behavioural therapy may be helpful

Pregabalin 75mg qd (evening)에 dramatic response (vas 10→3), 유해반응
- 구토 및 약 많지 않음
- 75mg bid에 vas 1→2 정도로 잘 나아짐

Learning points

- Secondary FM is common in pts with rheumatic dis.
- it should be suspected in pts with a lot of tenderness or tender joints
- but no synovitis and no acute phase response.
- Pts with FM are more likely to complain of s/e from medications (not easily distinguishable from sx of FM causing confusion).
- Careful evaluation and discussion are needed regarding stopping what might have been effective tx for inflammatory condition.
SNRI에 어느 정도 통증이 호전되었으나 (vas 10 → 6) 반비 및 구각질로 안해 통증을 더 풀리지 못함.

Pregabalin 75mg bid 추가 후 vas 6 → 2로 통증이 많이 감소되고 수면장애도
нем이 개선됨. 지속되는 반비 및 구각질 SNRI 증상 풀이고 pregabalin 약 75mg-150mg으로 약간 증량 후, SNRI 유약 반응 없이 통증은 계
속 잘 조절되고 있음.

**Learning points**

- FM may sometime develop in pts with chronic localized
  musculoskeletal pain such as myofascial pain, neck or low back pain,
  and atypical chest pain.
- It has been postulated that in these pts ‘sensory spreading’ from
  central sensitization may be the underlying pathophysiological process.
- The combined use of pregabalin along with SNRI could be considered
  because of their mechanism of action and adverse effect.

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**Summary I**

- None of our pharmacological treatments of chronic pain have anything more than modest efficacy when used as stand-alone therapy
- There are several treatments (e.g. CBT, exercise) that can lead to significant improvement in symptoms and function that are rarely utilized in routine clinical practice
- FM is a polygenic disorder. There will be sub-groups of FM needing different treatment.
- Depression-driven FM should be referred to a psychiatric team for management.

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**Summary II**

- Secondary FM is common in pts with rheumatic dis. It should be suspected in pts with a lot of tenderness or tender joints but no synovitis and no acute phase response.
- FM may sometime develop in pts with chronic localized musculoskeletal pain.
- The combined use of pregabalin along with SNRI could be considered because of their mechanism of action and adverse effect.