Pathogenesis of fibromyalgia

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INTRODUCTION — Fibromyalgia (FM) is a chronic pain disorder with unknown etiology and unclear pathophysiology [1,2].

There is no evidence that a single event “causes” FM. Rather, many physical and/or emotional stressors may trigger or aggravate symptoms. These have included certain infections, such as a viral illness or Lyme disease, as well as emotional or physical trauma [1-3].

A detailed description of the clinical manifestations of FM and an approach to the diagnosis of FM in adults and children are presented separately. (See "Clinical manifestations and diagnosis of fibromyalgia in adults" and "Fibromyalgia in children and adolescents: Clinical manifestations and diagnosis").

FM is only one of many causes of widespread pain. A discussion of the differential diagnosis of FM and the broad differential diagnosis is presented separately. (See "Differential diagnosis of fibromyalgia").

PATHOGENESIS — Fibromyalgia (FM) is considered to be a disorder of pain regulation, classified often under the term central sensitization [1,2,4] (see 'Altered pain processing' below). FM shares several features with other common pain disorders that are considered to be more central rather than peripheral pain conditions, such as migraine, tension headaches, temporomandibular joint disorder, and irritable bowel syndrome; these features include common genetic and central nervous system pain processing characteristics. More limited studies have suggested there might also be a role for peripheral neuropathic mechanisms or focal tissue changes in some patients. (See 'Peripheral pain mechanisms' below.).

During much of the 20th century, FM was thought to be a muscle disease. However, controlled trials found no evidence for significant pathologic or biochemical muscle abnormalities [1-3,5,6]. As an example, measures of muscle function, including force generation and lactate production
during exercise, and muscle pain following exertion are remarkably similar in women with FM and sedentary female controls [7,8]. Most investigators now believe that any muscle pathology is secondary to pain and inactivity rather than primary in nature [1,6-8]; however, some reports suggest that oxidative stress and mitochondrial dysfunction may play a role in the disease process [9].

Genetic predisposition — A number of observational and biologic studies suggest that chronic widespread pain and FM have, in part, a genetic basis [10]. First-degree relatives of patients with FM are 8.5 times more likely to have FM than relatives of patients with rheumatoid arthritis [11]. Familial aggregation of lowered thresholds for pressure-induced pain has been documented in first-degree relatives of patients. Such reports suggest a shared hereditary factor that may account for the overlap of chronic pain and mood disorders in families. However, no association between chronic widespread pain and any candidate gene has yet been conclusively documented [12].

Candidate genes — The ability of some antidepressant drugs to improve symptoms suggested that genes involved in serotonin and/or catecholamine metabolic or signaling pathways might be candidates for conferring susceptibility. Initial studies failed to identify significant associations between FM and three genetic markers with hypothesis-driven clinical relevance [13]. Examples of studies of genes involving these pathways include the following:

• Human serotonin transporter gene – An increased propensity to have inherited deletions in the gene for the human serotonin transporter suggests an underlying genetic component for the heightened pain sensation [14,15]. However, this putative association may be limited to patients with concomitant affective disorders, as it was not confirmed in patients with FM without depression or anxiety [16]. For example, there was no evidence for abnormal polymorphism of the serotonin transporter gene in one report in FM [17].

• Catecholamine methyltransferase genes – Catecholamine methyltransferase (COMT) genes that have been incriminated in predisposition to both pain and depression have also been implicated in FM [18]. There was an association between FM and the COMT val (158) met polymorphism, and the effect of the COMT genotype correlated with the number of pressure points reported [19]. Also, unaffected relatives of the FM patients had a reduced percentage of the COMT met allele.

Another report suggested an interaction in FM for COMT and correlated the genetic influence with pain levels [20]. FM patients with met/met COMT genotype experienced a greater decline in positive effect on days when pain was elevated than did either val/met or val/val individuals.

DRD3 Ser9Gly polymorphism was found to influence DNIC efficacy and pain tolerance in FM patients [21].

• Polymorphism of adrenergic receptors – There has been evidence for the association of FM and symptom severity with various adrenergic receptor gene polymorphisms [22]. Additional studies have identified selected genes of interest. A much larger candidate gene study than that described above evaluated 496 FM patients and 348 chronic pain-free controls [23]. Significant differences in allele frequencies between FM cases and controls were observed for three genes: GABRB3 (rs4906902, $p = 3.65 \times 10^{-5}$), TAAR1 (rs8192619, $p = 1.11 \times 10^{-5}$), and GBP1 (rs7911, $p = 1.06 \times 10^{-7}$). These three genes and seven other genes with suggestive evidence for association were examined in a second, independent cohort of FM patients and controls.
genotyped using the Perlegen 600K platform. Evidence of association in the replication cohort was observed for TAAR1, RGS4, CNR1, and GRIA4 genes.

The first genome-wide linkage scan for FM was performed in a cohort of 116 families from the Fibromyalgia Family Study [24]. The estimated sibling recurrence risk ratio for FM was 13.6, based upon a reported FM population prevalence of 2 percent. Genome-wide suggestive evidence of linkage was observed at markers D17S2196 and D17S1294 on chromosome 17p11.2-q11.2. These markers have potential impact on various pain pathways.

A more limited number of studies have focused on genes other than those involved in pain pathways. One study using whole exome sequencing found evidence in their cohort of a gene variant in 13 percent of FM patients that was associated with increased plasma levels of monocyte chemoattractant protein (MCP)-1 and interferon gamma induced protein (IP)-10, compared with patients with FM who had the wild-type allele; and another variant in 11 percent of patients that was associated with elevated levels of interleukin (IL)-12 compared with patients carrying the wild-type [25].

Altered pain processing — Alterations in pain and sensory processing in the central nervous system are present in FM [26]. Patients perceive noxious stimuli, such as heat, electrical current, or pressure, as being painful at lower levels of physical stimulation than do healthy controls [1,2,5,27].

Evidence of altered pain processing includes the following:

● Temporal and spatial summation of pain – FM patients experience greater than normal increases in the perceived intensity of pain when rapidly repetitive short noxious stimuli are administered, which is termed temporal summation of pain [28]. Spatial summation of pain, in which increasing the area of noxious stimulation results in a decreased pain threshold or an increase in perceived pain intensity, may also play a role in FM [28,29].

● Decreased endogenous pain inhibition – Endogenous analgesic systems appear to be deficient in FM [26,30]. There are both a reduction in diffuse noxious inhibitory control (in which decreased pain occurs upon stimulation with a second acutely painful stimulus) and an inability to inhibit irrelevant sensory stimuli following repetitive nonpainful stimulation [29,31].

● Pain receptors and pain-related neuropeptides – Changes are seen in opioid receptors, including upregulation in the periphery and a reduction in the brain [32,33]. Substance P, a neuropeptide associated with chronic pain states, is increased in the cerebrospinal fluid compared with controls [34]. Increased brain and plasma brain-derived neurotrophic factor have been found in FM [35].

● Functional neuroimaging – Differences in activation of pain-sensitive areas of the brain have been demonstrated by functional neuroimaging techniques, such as functional magnetic resonance imaging [36-39]. Areas of the brain that consistently exhibit greater activation after the same stimulus in FM patients than controls include the secondary somatosensory cortex, insula, and anterior cingulate cortex [26].

More limited data, using positron emission tomography, have shown reduced dopaminergic activity in the response to pain in patients with FM compared with controls [40,41].

Functional MRI was used to compare brain activity during the anticipation of pain with the amount of the impending pain in FM, RA, and control patients [42]. A unique temporal brain activation of the frontal cortex was noted in patients with FM, and areas of the motor cortex and
the cingulate cortex presented a FM-specific relation between brain activity during pain anticipation and the magnitude of the subsequent pain experience.

- **Affective and cognitive factors** – Both affective and cognitive factors influence pain processing in the central nervous system [1,2,37]. Patients with FM and comorbid depression demonstrate increased cerebral blood flow in the amygdala and anterior insula, areas important in the affective pain response [37]. However, unlike FM, depression does not seem to affect the level of neuronal activation in sensory pain regions such as the secondary somatosensory cortex [37].

- **Morphometric analysis** – Morphometric analysis by magnetic resonance imaging in patients with FM shows, compared with healthy controls, a significant reduction in total gray matter volume and a threefold increase in age-associated loss of gray matter, suggesting premature aging of the brain [43]. The degree of loss was greater in patients with a longer duration of disease. Such gray matter loss, which is also reported in other chronic pain and stress-related disorders, was most prominent in regions related to stress and pain processing but was also seen in areas related to cognitive function. Another study revealed similar findings [44]. However, another group found no significant difference in gray matter between FM patients and controls when controlling for depression [45].

- **Using proton magnetic resonance spectroscopy, FM patients had significantly higher levels of glutamine within the right posterior insula compared with controls [46]. Elevated insular glutamate in FM is associated with experimental pain. Within the right posterior insula, higher levels of glutamate were associated with lower pressure pain thresholds.

- **Patients with FM were evaluated for cortical excitability and intracortical modulation using transcranial magnetic stimulation of the motor cortex [47]. The FM patients compared with controls had deficits in intracortical modulation of GABAergic and glutamatergic mechanisms.**

- **Using MR spectroscopy, FM patients showed higher levels of glutamate and a higher glutamine-glutamate/creatine ratio in the right amygdala compared with controls [48]. In the FM patients with more pain, fatigue and depressive symptoms inositol (Ins) levels were found to be significantly higher in the right amygdala and right thalamus.

- **Using proton MR spectroscopy, GABA levels in the right anterior insula were significantly lower in FM patients compared with healthy controls [49]. No significant differences between groups were detected in the posterior insula or occipital cortex. Within the right posterior insula, higher levels of GABA were positively correlated with pressure-pain thresholds in the FM patients.**

- **FM patients exhibited less robust activations during both anticipation of pain and anticipation of relief within regions commonly thought to be involved in sensory, affective, cognitive, and pain-modulatory processes [50]. Reduced reward/punishment signaling in FM may be related to the augmented central processing of pain and reduced efficacy of opioid treatments in these patients.**

- **FM patients showed a lack of pain reduction impact from a positive emotional context [51]. Compared with controls, there was less activation in the secondary somatosensory cortex, insula, orbitofrontal cortex, and anterior cingulate cortex during positive picture pain trials.**

- **Structural changes and functional connectivity of the brain during application of intermittent pressure-pain stimuli were compared between 26 patients with FM and 13 age- and sex-matched healthy controls [52]. The patients displayed a distinct overlap between decreased cortical
thickness, decreased brain volumes, and decreased functional regional coherence in the rostral anterior cingulate cortex. The structural changes correlated with duration of symptoms.

- A systematic review of imaging studies in FM found moderate evidence that central sensitization is correlated with a gray matter volume decrease in specific brain regions (mainly anterior cingulate cortex and prefrontal cortex) [53]. They found evidence of decreased functional connectivity in the descending pain-modulating system in FM patients.

Sleep abnormalities — Underlying central nervous system dysfunction is suggested by the sleep and mood disturbances noted in the majority of FM patients [1,2,54]. Phasic alpha sleep activity is most characteristic of FM [55]. An increase in cyclic alternating patterns of sleep has been noted in FM and has been correlated with the severity of symptoms [56]. Some data suggest that disordered sleep patterns precede the development of pain and that abnormal sleep and pain predict depressive symptoms [54].

A longitudinal study of 12,350 women in Norway who did not have musculoskeletal pain or physical impairments at baseline found incident FM in 327 women at follow-up [57]. There was a dose-dependent association between sleep problems and risk of FM, with an adjusted relative risk (RR) of FM of 3.43 (95% CI 2.26-5.19) among women who reported having sleep problems often or always, compared with women who never experienced sleep problems. Age-stratified analysis showed that women age ≥45 years who reported having sleep problems often or always had an adjusted RR of FM of 5.41 (95% CI 2.65-11.05), while the corresponding RR for women ages 20 to 44 years who reported having sleep problems often or always was 2.98 (95% CI 1.76-5.05).

Neurohormonal perturbations — Hyperactivity of the stress response, demonstrated by abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis, has been found using different baseline and provocative testing, although the precise nature of these changes has not been elucidated [58-63]. Some neurohormonal abnormalities have included:

- A correlation between cerebrospinal levels of corticotropin-releasing factor, sensory pain, and variation in autonomic function in FM that was not associated with chronic fatigue [60]. Altered HPA axis activity may be linked to childhood trauma, especially physical abuse [61].

- A strong correlation between cortisol levels and pain upon awakening and one hour after waking in patients with FM compared with controls [62]. Correlations were made between HPA axis function and lymphocyte glucocorticoid reaction in FM patients [64].

- Abnormal levels of growth hormone in some but not all reports [65]. There is no good evidence to suggest that there are alterations of sex hormones in FM [66].

Autonomic nervous system dysfunction — Abnormal function of the autonomic nervous system in those with FM is suggested by the following:

- Patients with FM have been found to have orthostatic hypotension, and increased pain was noted in response to tilt table testing. FM patients also had significantly abnormal values in a number of autonomic tests as determined by the Composite Autonomic Symptom Scale (COMPASS). (See "Evaluation of parasympathetic nervous system function".)

- Decreased responsiveness to beta-adrenergic stimulation in those with FM was demonstrated by in-vitro testing of beta adrenergic receptor mediated cyclic AMP generation [67]. The alterations of cardiovascular regulation that had been postulated to be pathologically important in FM are significantly affected by deconditioning [68].
In a study involving 58 women, including FM patients and healthy age-matched controls, urinary catecholamines and heart rate were assessed for a 24-hour period in a controlled hospital setting (including relaxation, a test with prolonged mental stress, and sleep) and during daily activity [69]. The catecholamine levels were lower in FM patients than in controls. Patients with FM had significantly lower adrenaline levels during the night and the second day and had significantly lower dopamine levels during the first day, the night, and the second day. Overall, heart rate was significantly higher in patients than in controls.

In another approach, plasma catecholamines, ACTH, and cortisol were reduced in 16 FM patients compared with 16 healthy controls as they performed static knee extension until exhaustion [70].

Nocturnal heart rate variability indices were significantly different in FM women compared with healthy individuals [71]. In FM patients, these HRV parameters correlated with several symptoms including pain severity.

Immune system changes — There is little evidence to support the concept that FM is an immune mediated disorder [1,2]. Autoantibodies with affinity for a 68/48 kD protein have been found in a subset of patients with FM but not in healthy controls [72]. Other cytokine changes have been reported, but studies have not been consistent or controlled well for mood disturbances and activity levels [73].

A meta-analysis concluded that the role of cytokines in FM is unclear [74]. In general, FM patients had higher serum levels of IL-1 receptor antagonist, IL-6, and IL-8 and had higher plasma levels of IL-8. Meta-analysis of eligible studies showed that FM patients had higher plasma IL-6 levels compared with controls (standardized mean difference = -0.34 [95% CI -0.64 to -0.03]). The majority of investigated cytokines did not differ between patients and controls.

Peripheral pain mechanisms — FM patients often have focal tissue abnormalities including myofascial trigger points, ligamentous trigger points, or osteoarthritis of the joints and spine. These are important peripheral pain generators that may initiate or perpetuate chronic pain [75]. Other studies have found evidence of peripheral neuropathic changes, including neurologic examination findings and reductions in epidermal nerve fiber density suggestive of small fiber neuropathy [76-79].

Examples of studies suggesting a role for peripheral pain mechanisms include:

- Sustained isometric muscle contraction recruits segmental and/or extra-segmental descending inhibition in healthy subjects but not in FM [80]. Descending pain modulation shifts from descending inhibition toward descending facilitation following muscle nociception in FM. Peripheral mechanical hyperalgesia and descending facilitation counterbalance the effect of descending inhibition in FM.

- Several studies have suggested that there may be a relationship in some patients between FM and small fiber neuropathy [76-79]. However, these studies have not carefully controlled for levels of physical fitness and activity, and some of the observed abnormalities could be a consequence of pain and deconditioning.

- A case-control study compared the function and morphology of small nerve fibers in 25 patients with FM syndrome with patients with depression and with healthy controls [76]. Patients with FM syndrome had increased levels of neuropathic pain based upon responses to questionnaires designed to assess this type of pain. Additionally, patients with FM syndrome but not patients
with depression had impaired small fiber nerve function compared with controls, demonstrating increased cold- and warm-detection thresholds in quantitative sensory testing, increased N1 latencies upon stimulation at the feet, and reduced amplitudes of pain-related evoked potentials upon stimulation of face, hands, and feet. In skin biopsies, total and regenerating intraepidermal nerve fibers at the lower leg and upper thigh were reduced in patients with FM syndrome compared with the control subjects. Accordingly, a reduction in dermal unmyelinated nerve fiber bundles was found in skin samples of patients with FM syndrome compared with patients with depression and with healthy controls, while myelinated nerve fibers were spared.

• A study involving 27 patients with FM and 30 controls found that a significantly greater proportion of patients with FM had abnormal skin biopsies demonstrating findings consistent with small fiber peripheral neuropathy (41 versus 3 percent), suggesting that an underlying small-fiber polyneuropathy may cause symptoms sometimes identified as being due to FM [77]. Another uncontrolled study of patients referred for the evaluation of primary FM without associated medical comorbidities identified 6 of 20 patients who met criteria for small fiber neuropathy; electrodiagnostic studies were normal in all patients [78].

• A study involving 41 patients with FM and 47 healthy controls reported findings suggestive of both a diffuse and a length-dependent neuropathic process [79]. There was evidence of stocking distribution hypesthesia in all patients with FM, Mean calf and thigh epidermal nerve fiber density (ENFD) was reduced in the group with FM compared with the controls, although there was substantial overlap in the values. Other results included a weak but statistically significant inverse correlation between calf ENFD and age in the FM patients but not the controls. Among several immunologic studies that were performed the one abnormality noted was an inverse correlation between calf nerve fiber density in FM and serum levels of the IL-2 receptor.

• Some studies have suggested that metabolic changes may be present in the muscle of patients with FM [81]. In one study, comparing 19 patients with FM and 14 controls, concentrations of adenosine triphosphate (ATP) and phosphocreatinine (PCr) were significantly lower (28 to 29 percent) in quadriceps muscle in the patients with FM [81]. The quadriceps muscle fat content was significantly greater in the patients with FM, who also exhibited lower physical capacity in the hands and legs, which correlated with the reduced concentrations of ATP and PCr. These findings were consistent with changes that could result from a combination of inactivity related to pain and muscle mitochondrial dysfunction.

SUMMARY

• There is conclusive evidence that alterations in central nervous system pain processing are responsible for many of the features of fibromyalgia (FM). (See 'Pathogenesis' above and 'Altered pain processing' above.)

• Genetic and environmental factors likely interact to promote a state of chronic central and peripheral nervous system hyperirritability. (See 'Genetic predisposition' above and 'Candidate genes' above.)

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REFERENCES


