ABSTRACT
Fibromyalgia is a symptom complex syndrome most commonly seen in women. The exact incidence of the disease is yet to get worked out in India, but a fair incidence has been reported in western literature to 3.6%. Till no definite criteria have been laid for the diagnosis of FM. American Rheumatologic Association (ARA) has laid out some criteria and diagnostic points, but they are being modified now. It appears that this disorder is a manifestation of abnormal pain perception in the central level of pain perception rather than the peripheral joints or muscles, a phenomenon known as allodynia. Treatment is mainly concentrated toward alleviation of symptom complex, but definite management is yet to be tailored.

RECENT CONCEPTS IN PATHOPHYSIOLOGY
Fibromyalgia is late recognized to be a disorder of central pain processing, or recognizing syndrome, depending on the central sensitivity of the inputs, whether nociceptive or non-nociceptive. Clauw describes FM as a diffuse problem of sensory “volume control”. He observes that the FM patients’ pain threshold is very low, so that non-nociceptive sensory stimuli such noise, visual, touch and odors are observed painful. This happens because of hypervigilance centers in the brain pain centers with neurobiologic changes due to altered neuropeptides.

Researchers in FM syndrome observed biochemical, metabolic and immune regulatory dysfunctions, which make one to think that it is no longer a subjective pain condition.

It appears that differential appreciation of nociception and afferent input from somatic reflexes, which are modulated by emotional, motivational and cognitive aspects of pain often helps to discriminate the pain threshold and quality of pain. These differentiating aspects appear to have lost in FM syndrome.

In addition to strictly sensory-discriminative elements of nociception and afferent input from somatic reflexes, major contributions from pathways and regions of the brain that are associated with emotional, motivational and cognitive aspects of pain are evident and help determine the subjective intensity of pain.

The two principal effectors of the stress response, the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system (SNS), are also activated.

It appears that the patients are normally adaptive, but the stress response will become maladaptive in patients who also suffer from chronic pain, fatigue syndromes, which could be designated along with FM. Negative emotions, psychological factors, beliefs, attributions can act as triggering point as stressors precipitating FM syndrome complex, as it amplifies the pain syndrome especially in women. Patients with FM who manifest with such emotional disturbances, resulting in neuroendocrine disorders, lead to flu-like syndromes, diffuse pain all over the body and poor sleep situations. The important biologic elements here include proinflammatory cytokines, the HPA axis, other neuroendocrine axes and the autonomic nervous system.
Chapter 96  Fibromyalgia: Does it Exist? If so, What is the Management?

Flow chart 1: Algorithm for fibromyalgia

Suspected fibromyalgia

Look for tender points
Assess the underlying comorbid situations—psychological background

Routine biochemical and endocrine Na, K, Ca assessment

With sleep disorder
Melatonin 3 mg + zolpidem or Anxiolytic drugs and/or Duloxetine or Pregabalin 60 mg titrate with psycho counseling

Without sleep disorder
Anxiolytic drugs and/or Duloxetine or Pregabalin 60 mg titrate with psycho counseling

No analgesics and steroids would be of any help
Correct abnormalities, endocrine, minerals, electrolytes, if any
Vague evidences on anticonvulsant drugs as remedy are available
Finally cognitive and behavioral therapy should be applied in refractory cases

Spinal inputs all types
- Emotional/motivational
- Autonomic
- Discriminative
- Motor/reflex

- Dysregulated endogenous opioid analgesic response in several areas of brain dealing with pain modulation added to dopamine dysregulation
- Enhanced temporal summation of second pain generation

It is also observed that high throughout genotyping is in identifying a series of single nucleotide polymorphism (SNP) haplotypes that influence neuropeptide levels and receptor sensitivity in the brain, thus contribute to the various malperception of pain processing. Those SNP haplotypes contribute to the vulnerable elements in the development of FM and allied CSS. This concept helps to deal with FM pharmacologically, such as use of drugs like duloxetine, which increases the inhibitory neurotransmitters, or like gabapentin and pregabalin, which decrease the levels of excitatory neurotransmitters.

Growth hormone abnormalities are also thought to contribute to symptoms in FM. Non-nociceptive impulses such as touch and warmth are realized as nociceptive pain owing to enhancement of pain threshold, which can be proved with an algometry measuring scale.

Various types of abnormalities in pain perception and processing have been demonstrated with various research studies. Excessive pro-nociceptive excitatory peptides like substance P, glutamate, especially in insular cortex
Similarly low levels of inhibitory neuropeptides like serotonin, norepinephrine, in the antinociceptive pathways in posterior spinal column

Growth hormone, produced during delta sleep, is involved in tissue repair. Therefore, disrupted stage 4 (delta) sleep associated with FM may account for low levels of growth hormone. In FM, growth
hormone stimulates the production of insulin-like growth factor I (IGF-I) in the liver. Some authors have found that most patients with FM have low levels of IGF-I and that low levels are specific and sensitive for FM. Increased levels of nerve growth factors (NGFs) have been found, which enhances the sensitivity of substance P.

**COGNITIVE DYSFUNCTIONS IN FIBROMYALGIA**

It is observed that a definite decline in episodic, semantic, verbal and procedural skills memory in FM show a similarity to the levels of function in people who are older than them by 20 years. Another possible cause of cognitive dysfunction is the distracting quality of pain in FM. Cognitive performance of patients with FM is correlated with their reported level of pain. Other studies have implicated glial cell water retention and glial cell abnormalities as causes of cognitive dysfunction in FM.

Cognitive dysfunction has been linked to CNS imbalances. Abnormal levels of neurotransmitters such as substance P, serotonin, dopamine, norepinephrine and epinephrine may cause cognitive dysfunction. Neuroendocrine imbalance of the HPA axis may play a role along with the distracting quality of pain.

Fibromyalgia is very common in women, owing to their phasic gonadal pain modulating hormones’ maladaptation to the pituitary functions, poor pain adaptation and increased propensity to stress syndromes. They do have poor stress-induced analgesia and opioid system with high level of substance P.

**IMAGING IN FIBROMYALGIA**

1. Single-photon emission computed tomography (SPECT) scanning has defined abnormalities with decreased blood flow in the both caudate nuclei and thalamus.
2. More brain areas are extracted in functional magnetic resonance imaging (fMRI) in FM cases than normal controls, suggestive of collective efforts in alphabetization, with lower activation in attention networks, attracting other resources for help.

Engel’s biopsychosocial model of chronic illness (i.e. health status and outcomes in chronic illness are influenced by the interaction of biologic, psychological and sociologic factors) provides a useful way to conceptualize FM. The model is pictured in Figure 2.

**Biologic Variables**

Many of the biologic variance is inherited but they are uncertain in the genesis of FM. A probable link would be decreased collagen cross-linking, hypermobility, and environmental chemicals. Many issues related to the cortical and subcortical appreciation of pain could be related to the following:

- Anticipation of pain (medial frontal cortex, cerebellum)
- Attention to pain (dorsal anterior cingulate gyrus, dorsolateral prefrontal cortex)
- Emotional aspects of pain (claustrum, closely connected to the amygdala)

**Physical Examination**

Till now, there were no specific criteria to decide on the diagnosis of FM, and no considerable points were recognized in physical examinations till ARA laid criteria of diagnosis on physical examination (Figure 3).

**Site Locations of Tender Points as Specified by ARA**

The 18 possible tender points exist as nine pairs (in addition to 3 control sites), four on the anterior of the body and five on the posterior of the body. Tender points may be found in any palpable muscle, but 18 sites are consistently present in patients with FM. But of late ARA, has disagreed in testing all the 18 points, as it would be more painful for the patients with remote practicality and unreliability especially when psychogenic allodynia dominates over this disease. Hence, testing for one or two tender points would be useful.

**Pressure Algometry**

A reasonable tool for quantification of pain perception and pain tolerance is the pressure algometer or dolorimeter. It provides a simple assessment tool for the pain in the suspected tender points in FM. Normal values are 4 kg/cm² and allodynia represents pain perception less than the normal. It is more useful tool in the follow-up of treatment in FM.

**DIFFERENTIAL DIAGNOSIS**

- Thyroid and parathyroid dysfunctions
- Diffuse osteoporosis
- Certain viral myositis
- Polymyositis
- Personality disorders
• Regional pain syndromes
• Polymyalgia rheumatica
• Post-traumatic stress disorder (PTSD)
• SLE
• Dermatomyositis
• Paget’s disease
• Malignancy-associated syndromes
• Infectious chronic viral syndromes and other painful syndromes.

Recently, it has been reported that mitochondrial myopathy presented with syndrome of FM.  

MANAGEMENT

Most of the drugs in FM are designed in such a way to interfere with the central pain processing modules, and it is strange that analogous and anti-inflammatory drugs react very little. This again makes one think that the problem appear to be central than peripheral. The common drugs used are as follows.

For a long time, dextromethorphan, an N-methyl-D-Aspartate (NMDA) receptor was tried for a long time. Beta-blockers found to be of slight use. The US Food and Drug Administration has approved Pregabalin for this neuropathic pain associated with FM, along with Milnacipran as antidepressant. Among the analgesics, opioid like Tramadol, which has additional effects on serotonin and norepinephrine receptors, moderately improves tolerance to the pain especially in patients with allodynia. Selective estrogen receptor modulatorRaloxifene 60 mg every alternate day has some effect in reducing the tender point count, especially in postmenopausal women. Experimental data suggest that the synthetic cannabinoid nabilone in doses escalating from 0.5 mg daily to 1 mg twice daily improves the tolerance to pain and reduces the anxiety related to FM. Other drugs are vitamins, minerals, malic acid with magnesium, antioxidants and amino acids.

The associated depression and anxiety state has to be managed with psychotherapy, mood elevators and anti-anxiety drugs. A moderate doses of alprazolam, etizolam, short-acting hypnotics especially combination of melatonin with Zolpidem (Zolosan; melatonin 3 mg with 5/10 mg zolpidam) with good advice for sleep hygiene would be useful in the management of sleep disturbances in FM. Sodium oxybate is an inhibitory chemical neurotransmitter in the brain acting on specific receptors for gamma hydroxybutyrate (GHB) and gamma aminobutyric acid (GABA). Sedative and hypnotic prolongs stage III/IV restorative sleep in FM. Other drugs tried are like Trazodone, (which inhibits serotonin uptake by brain synaptosomes), busiprone and temazepam.

Skeletal Muscle Relaxants

Most of the skeletal muscle relaxants have short-term benefit except cyclobenzaprine, which has long-term improvement over placebo as a single night time dose in combination with anxiolytic drugs. Cyclobenzaprine acts centrally and reduces the somatic tonic signals, influencing alpha and gamma motor neurons, but not very beneficial in FM. Other drugs approved by FDA are Pramipexole and Gabapentin in restless leg syndrome with FM.

Psychosocial and behavioral therapy finds a place in the management of FM, along with the following:

• Relaxation training
• Activity pacing
• Guided imagery
• Written emotional disclosure
• Distraction strategies
• Instruction in proper sleep hygiene.

PROGNOSIS

Fibromyalgia is a chronic relapsing condition, and reversing the allodynia and hyperalgesia may be impossible. Tachyphylaxis as well progressive decrease in the response to therapy is also noted. Hence the treatment goal is restricted to least response to therapy and improvement in day to day activity. A prospective study from Denmark reported a 10 fold increased risk of death from suicide in patients with FM who were followed for as long as 16 years. This study also found a 6 fold increased risk of liver cirrhosis/biliary tract disease and a 3 fold increased risk of cerebrovascular disease. This association also needs to be studied in other populations.

CONCLUSION

Whatever may be the situation, the physician is bound to manage cases of FM, which is really a practical challenge. It is often found that the patient changes the physicians, various specialists, and ultimately when the psychosocial aspects overwhelms as a problem in their life, which is more important, they often forget the syndrome of FM.

REFERENCES