STATE-OF-THE-ART ON FIBROMYALGIA MECHANISM

Jaime C. Branco*

Abstract

Fibromyalgia syndrome (FMS) is a very prevalent disorder defined by the presence of hyperalgesia and allodynia that leads to musculoskeletal chronic pain very frequently associated with fatigue and a diversity of other symptoms. The cause of FMS is unknown and its pathogenesis is complex and not well understood. This paper will rather discuss central pain mechanisms and the role of stressors and other factors as triggering events for onset of clinical manifestations.

Keywords: Fibromyalgia Syndrome; Pathogenesis; Central Pain Mechanisms; Stressors.

Fibromyalgia syndrome (FMS) is a common chronic disorder characterized by diffuse musculoskeletal pain and fatigue. Pain is referred to soft tissues (e.g. muscles, tendons, ligaments, bursae) but apparently is not associated with inflammation or any other morphologic damage or metabolic disturbance on peripheral tissues. The etiology of FMS is unknown and its pathophysiology unclear. Patients with FMS present a multiplicity of clinical complaints (e.g. chronic musculoskeletal widespread pain and other painful entities, fatigue, sleep disorders, morning stiffness, cognitive dysfunction, mood disturbances, irritable bowel syndrome, non-dermatomal paresthesias and many other less frequent clinical manifestations). In opposition, except for tender points, objective signs on physical examination are absent and all laboratory and imaging diagnostic tests are normal or negative. Several medical conditions and diseases (e.g. systemic/inflammatory rheumatic diseases, psychiatric illnesses, neurologic disorders, and infectious diseases) occur frequently with FMS. These coexisting medical conditions may worsen and/or perpetuate patients' symptoms[1-3].

The pathogenesis of pain and other manifestations in FMS is very complex and not well understood. The important question is what type of mechanisms explains this disturbing clinical entity.

FMS Predisposition

FMS is mainly characterized by allodynia (painful response to a normally innocuous stimulus), hyperalgesia (extreme reaction to an usually painful stimulus), increased pain persistence and enlarged referred painful areas.

Patients with FMS have an abnormal pain experience due to an altered pain processing[4,5]. Several 'peripheral' (e.g. skin, microvessels, and muscle) abnormalities were described in FMS. None of these changes are specific of FMS, although most of them can be responsible for, or related to repetitive nociceptive inputs, which can trigger a phenomenon called neuroplasticity, and may also be involved in the maintenance of these central nervous system changes[4]. So, apart from these non-specific structural and functional peripheral abnormalities, some undetected peripheral sensitization disorders, or aberrant peripheral nervous transmission may be considered on FMS mechanisms[4]. Based on many very well developed FMS studies, there is now sufficient evidence to consider a neuropathophysiological basis for the abnormal pain processing leading to its increased perception[5].

There are a large number of factors conditioning the onset and maintenance of FMS. Among these, genetic circumstances and environmental aspects are crucial for the development of this condition. Increasing evidence suggests a genetic predisposition in FMS. First degree relatives of patients with FMS have an 8-fold increased risk of developing this disorder compared to patients with rheumatoid arthritis[6]. The most probable way of transmission is polygenic[7]. Among the candidate genes several studies confirm that those related to seroto-

*Professor Associado com Agregação de Reumatologia da Faculdade de Ciências Médicas (FCM) da Universidade Nova de Lisboa (UNL); Investigador Principal do Centro de Estudos de Doenças Crónicas (CEDOC), FCM da UNL; Director do Serviço de Reumatologia do CHLO, EPE/Hospital Egas Moniz

nin play a more relevant role in FMS (e.g. serotonin transporter, 5-hydroxytryptamine 2A receptor). According to other data, FMS may be related to catecholamine (e.g. catecholamine-o-methyltransferase), and dopamine (e.g. dopamine D4 receptor) polymorphism genes[8,9]. All these monoamines play an important role in both stress response and sensory pathway systems.

In one or multiple life moments some environmental stressors may interact with genetically determined factors. In individuals at risk, FMS may be precipitated by an external insult (e.g. trauma, infections, and diseases), an emotional stressor or psychosocial events. These precipitating factors may be acute or chronic. After FMS onset its manifestations can be maintained through perpetuating factors related to lifestyle, professional activity, physical conditioning, hypervigilance, mood disorders, catastrophizing or coping behaviours[10].

Central Pain Mechanisms

The sequence of events causing FMS is not clear, but it certainly implicates biochemical and metabolic abnormalities. Some of the changes seen in the CNS (e.g. low levels of serotonin, significant increase of nerve growth factor and elevated concentrations of substance P) strongly suggest that FMS is not a subjective pain condition, contrarily indicating the presence of an abnormal central processing of nociceptive pain. In fact, FMS patients have several central sensitization characteristics[11].

Some authors describe FMS in terms of a sensory intensity control disorder as many patients show a low threshold, not only to pain but also to other sensitive stimuli, such as noise, odours, flavours and light[12].

Repetitive noxious stimulation may result either in habituation, with reduced painful responses, or sensitization, with increased algic response. Therefore, the prolonged and/or intense activity of the dorsal horn neurons caused by repetitive or sustained noxious stimulation may result in increased neuronal response or central sensitization[13]. This means that CNS may learn, and therefore may also change. Thus, chronic pain characteristics change over time. Oppositely, pain is able to change CNS 'response', which results in a phenomenon called neuroplasticity[11]. This neuroplasticity and subsequent CNS sensitization includes changes in terms of function of its various systems (e.g. chemical, electrophysiological), which causes allodynia and hyperalgesia[11]. Central sensitization is a pathophysiologic mechanism that is common to and unifies the concept for FMS and other related, similar and overlapping syndromes (e.g. chronic headaches, irritable bowel syndrome, temporomandibular disorder, restless legs syndrome, multiple chemical sensitivity, interstitial cystitis, primary dysmenorrhoea, "functional" chronic pelvic pain, depression) without demonstrable structural pathology.

What defines central sensitization is the increased response to stimulation, which is mediated by CNS signalling amplification. In order to occur, it must recruit a mechanism that signals a noxious response, even if aggression was not harmful[14]. This nervous system dysfunction can amplify normal peripheral pain and this phenomenon may involve the spinal cord and the thalamus[15]. Central sensitization involves spontaneous nerve activity, expanded receptive fields – with larger topographic distribution of pain – and augmented stimulus response, such as abnormal temporal summation or 'wind-up'[16,17]. 'Wind-up' is a central spinal cord mechanism in which repetitive noxious stimulation results in a slow temporal summation that is sensed in humans as increased pain[18]. Spinal cord amplification mechanism of pain is related to temporal summation of 'second pain' or 'wind-up'. This 'second pain' is more sustained and mainly related to chronic pain, although it may occur in all individuals it is more intense in patients with FMS[19].

During stimuli transmission, as 'second pain', by C fibers, N-methyl-D-aspartate (NMDA) receptors of the second neurons are activated[19]. NMDA amplifies calcium influx into dorsal horn neurons, which leads to nitric oxide synthetase activation. Nitric oxide synthesis induces the release of substance P and other neuropeptides of pre-synaptic neurons, which facilitate hyperalgesia and central sensitization maintenance[20,21]. Substance P reduces synaptic excitability threshold and expands nociceptive fields and neuronal activation by non-nociceptive afferent impulses[22].

Dysregulation of descending inhibitory pain pathways may also be related to algic sensitization. In healthy individuals brain signals downregulate spinal cord responses to painful stimuli[23]. This modulatory response is also known as diffuse noxious inhibitory controls (DNIC)[24]. In patients with FMS, pain modulation after application

of noxious stimulation is absent, and pain facilitating descending pathways may be very relevant[25].

Glial cells are known to play an important role in pain signalling modulation[26]. Glial cells are activated by painful stimuli and pain signalling neurotransmitters. These cells express receptors, not only for neurotransmitters but also for viruses and bacteria, and when activated by painful stimulus, release a group of neuroactive substances like prostaglandins, leukotrienes, nerve growth factors, nitric oxide and excitatory amino acids. Astrocytes and glial cells also release pro-inflammatory cytokines (e.g. TNF-alpha, interleukin-1 and -6). All these phenomena can increase signalling and perception of pain and may cause expansion of pain fields[27,28].

Neurohormonal disturbance in FMS involves above all dysfunction of the hypothalamic-pituitary-adrenal axis. This axis plays a central role in physiologic response to stress[29]. FMS patients have low 24-hour serum cortisol levels and an abnormal circadian pattern of cortisol concentration. They also show blunted serum cortisol response to endogenous CRH, which suggests an abnormal response to stress and also an inadequate reaction to several stressful events[30-33].

Growth hormone levels are reduced during sleep, probably due to the disruption of stage IV sleep, well documented in the majority of FMS patients[34]. Sex hormone secretion is apparently normal[35].

Also, changes in neurotransmitters are certainly involved in FMS pain aberrant processing. Serotonin is derived from tryptophan, is widely distributed and has inhibitory effects on several pain pathways. Measurements of serum and CNS serotonin levels have not shown consistent results[36,37].

Although investigations on the role of dopamine in FMS mechanism have been neglected there is an increased body of evidence of a dopamine-related pathology in FMS patients[38].

Evidence of Central Sensitization in FMS

Studies in FMS patients versus healthy controls clearly showed exaggerated pain responses after sensory (e.g. thermal) stimulation of healthy tissues[39]. Intramuscular electrical stimulation (used to assess the efficacy of temporal summation) caused more severe pain and larger referred areas in FMS patients compared to controls[40].

Also, compared to controls, FMS patients showed more intense and long-lasting pain sensation after painful experience[17]. This prolonged and amplified decay supports the presence of central sensitization[22].

In FMS patients, pain inhibitory systems are not normally recruited, which did not occur in healthy controls and patients with chronic low back pain[39,41]. Also, compared to controls, FMS patients presented a lack of activation of endogenous inhibitory systems[42].

All these investigations suggest that FMS is a disorder of pain sensitivity modulation. These results are based on patients' reports of pain, and are consequently of subjective nature. Therefore, we must consider whether hypersensitivity is the result of central mechanisms or the cause of hypervigilance. Nevertheless, we have now objective data on the existence of central sensitization in FMS.

R. Gracely et al used functional magnetic resonance imaging (fMRI) to evaluate the pattern of cerebral activation during application of painful pressure, and to determine whether this pattern was augmented in patients with FMS compared to controls. They found that comparable subjectively painful conditions resulted in activation patterns that were similar in patients and controls, and similar pressures resulted in different regions of activation and greater effects in patients. To these authors, these results support the claim that FMS is characterized by cortical or subcortical augmentation of pain processing[43]. Two groups of investigators, JA Desmeules et al (2003) and B Banic et al (2004) used spinal nociceptive flexion reflex, a specific physiologic correlation for the objective evaluation of central nociceptive pathways. Electrical stimulation that was used bypass peripheral receptors. These studies, although indirectly, strongly pointed to the existence of a state of central hyperexcitability of the nociceptive system in FMS patients[44,45]. In December 2008, J Lutz et al published in Arthritis and Rheumatism a very interesting study using a combination of two different magnetic resonance (MR) techniques – MR diffusion-tensor imaging (MR-DTI) and MR of voxel-based morphometry (MR-VBM) – to determine microstructure and volume changes in the central neuronal networks involved in the sensory-discriminative and affective-motivational characteristics of pain, anxiety, memory and regulation of stress response in FMS female patients and healthy

female controls. Both methods demonstrated a striking pattern of changes in brain morphology among patients with FMS. Thalami and thalamocortical tracts and insular regions showed significant decreases in fractional anisotropy. In contrast, post-central gyri, amygdalae, hippocampi, superior frontal gyri and anterior cingulated gyri presented increases in fractional anisotropy and decreases in gray matter volume. MR-DTI seems to be more sensitive than MR-VBM regarding visualization of brain microstructural changes in these patients[46].

Other Pathophysiologic Factors

Abnormal function of the autonomic nervous system is also suggested in FMS in view of the following findings: 1) orthostatic hypotension and increased pain in response to tilt table testing; 2) increased rest supine heart rate and decreased heart rate variability reported in both female and male patients; 3) decreased responsiveness to beta-adrenergic stimulation in FMS patients (demonstrated in vitro), and, 4) changes in cardiovascular regulation that are probably pathologically relevant in FMS and significantly affected by deconditioning[47-51].

Quantitative and qualitative sleep disturbances are very common in FMS patients. Phase-IV sleep deprivation led to FMS symptoms in healthy controls. All the more prevalent findings on polysomnography (e.g. alpha intrusion, fewer sleep spindles, poor sleep efficiency, increase in cycle alternating pattern rate) are also found in normal individuals and in patients with other disorders. Sleep abnormalities do not correlate to FMS complaints, and treatment of sleep problems rarely leads to the improvement of FMS symptoms[52-54].

Psychopathology plays a crucial role in some but not all patients with FMS. In general, FMS patients and close family have a larger prevalence of psychiatric comorbid conditions than controls with other rheumatic diseases. Nevertheless, most patients with FMS are not clinically depressed, and depression is therefore an independent overlapping condition[55]. Only about one third of FMS patients are clinically depressed at each consultation and two thirds in all long lasting FMS duration. Convincing binding factors to link FMS and depression are lacking, but depression is significantly more common in FMS patients than in patients with other musculoskeletal disorders[56].

Much has been said and written on the connection between depression and FMS[57]. Pain and depression share common pathways and neurotransmitters. This is a possible explanation for their reciprocal relationship. In practice, the presence of depression aggravates pain and vice versa[57].

Cross-sectional studies in FMS patients have shown increased rates of anxiety and somatization, although it was not possible to determine whether the psychiatric comorbid condition 'caused' FMS in these patients or, on the contrary, the painful condition resulted in emotional distress[58].

Conclusions

Although chronic pain in FMS is perceived in soft musculoskeletal tissues, any of the abnormalities described in peripheral structures are specific or exclusive of this condition. Additionally, there is an increasing body of evidence suggesting the existence of an abnormal central pain processing in FMS. Some of these central dysfunctions could even be demonstrated in FMS – hyperexcitability of spinal cord, reduced perfusion of pain-related brain areas, changes in brain morphology, and high levels of substance P in CSF.

Several mechanisms may be involved – neurotransmitter abnormalities, neurohormonal dysfunction, central sensitization, dysregulation of descending inhibitory pain pathways – in FMS pathophysiology. All these mechanisms are probably more concurrent than competitive or exclusive on pain amplification. Genetic and environmental factors are ultimate contributors, which predispose individuals to FMS.

Several stressor events are triggering factors to the onset of FMS clinical manifestations[59]. Other conditions like mood and anxiety disorders may modulate pain processing in FMS patients. Finally, FMS symptoms can lead to maladaptive behaviours and decreased function, which may further worsen patients' symptoms.

Much of this knowledge on FMS pathology is questionable and needs further research with better controlled studies to be validated and transformed in solid science. The incomplete understanding of FMS pathophysiology conditions its actual treatment. FMS symptoms must be pharmacologically managed, and non-pharmacologic therapies should be used to control dysfunction[60].

Correspondência para
Jaime C. Branco
Serviço de Reumatologia
CHLO, EPE/Hospital Egas Moniz
Rua da Junqueira, 126
1349-019 Lisboa
E-mail: jaime.branco@fcm.unl.pt

References

1. White KP, Harth M, Speechley M, Ostbye T. Testing an Instrument to Screen for Fibromyalgia Syndrome in General Population Studies: The London Fibromyalgia Epidemiology Study Screening Questionnaire. J Rheumatol 1999; 26: 880-884
2. Wolfe F, Smythe HA, Yunus MB et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: Report of the Multicenter Criteria Committee. Arthritis Rheum 1990; 33: 160--172
3. Wolfe F, Ross K, Anderson J et al. The Prevalence and Characteristics of Fibromyalgia in the General Population. Arthritis Rheum 1995; 8: 19-28
4. Bengtsson A. The Muscle in Fibromyalgia. Rheumatology 2002; 41: 721-724
5. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative Review: The Pathophysiology of Fibromyalgia. Ann Intern Med 2007; 146: 726-734
6. Buskila D, Neumann I, Hazanov I, Carmi R. Familial Aggregation in the Fibromyalgia Syndrome. Semin Arthritis Rheum 1996; 26: 605-611
7. Buskila D, Sarzi-Puttini P, Ablin JN. The Genetics of Fibromyalgia Syndrome. Pharmacogenomics 2007; 8: 67-74
8. Offenbaecher M, Bondy B, de Jonge S et al. Possible Association of Fibromyalgia with a Polymorphism in the Serotonin Transporter Gene Regulatory Region. Arthritis Rheum 1999; 42: 2482-2488
9. Gürsoy S, Erdal E, Herken H et al. Significance of catechol-O-methyltransferase Gene Polymorphism in Fibromyalgia Syndrome. Rheumatol Int 2003; 23: 104-109
10. Clauw DJ & Chrousos GP. Chronic Pain and Fatigue Syndromes: Overlapping Clinical and Neuroendocrine Features and Potential Pathogenic Mechanisms. Neuroimmunomodulation 1997; 4: 134-153
11. Meeus M & Nijs J. Central Sensitization: A Biopsychosocial Explanation of Chronic Widespread Pain in Patients with Fibromyalgia and Chronic Fatigue Syndrome. Clin Rheumatol 2007; 26: 465-473
12. Yunus MB. Central Sensitivity Syndromes: A New Paradigm and Group Nosology for Fibromyalgia and Overlapping Conditions and the Related Issue of Disease versus Illness. Semin Arthritis Rheum 2008; 37: 339-352
13. Besson JM. The Neurobiology of Pain. Lancet 1999; 353: 1610-1615
14. Eriksen HR & Ursin H. Subjective Health Complaints Sensitization and Sustained Cognitive Activation (Stress). J Psychosom Res 2004; 56: 445-448
15. Elliott F. Aspects of 'Fibrositis'. Ann Rheum Dis 1944; 4: 22-25
16. Li J, Simone DA, Larson AA. Windup Leads to Characteristics of Central Sensitization. Pain 1999; 79: 75--82
17. Staud R, Vierck CJ, Cannon RL et al. Abnormal Sensitization and Temporal Summation of Second Pain (Wind-up) in Patients with Fibromyalgia Syndrome. Pain 2001; 91: 165-175
18. Gracely RH, Grant MA, Giesecke T. Evoked Pain Measures in Fibromyalgia. Best Pract Res Clin Rheumatology 2003; 17: 593-609
19. Mendell LM & Wall PD. Responses of Single Dorsal Cord Cells to Peripheral Cutaneous Unmyelinated Fibres. Nature 1965; 206: 97-99
20. Meller ST & Gebhart GF. Nitric Oxide and Nociceptive Processing in Spinal Cord Pain. Pain 1993; 52: 127--136
21. Luo ZD & Cizkova D. The Role of Nitric Oxide in Nociception. Curr Rev Pain 2000; 4: 459-466
22. Staud R. Evidence of Involvement of Central Neural Mechanisms in Generating FM Pain. Curr Rheumatol Rep 2002; 4: 299-305
23. Woolf CJ & Salter NW. Neuronal Plasticity: Increasing the Gain in Pain. Science 2000; 288: 1765-1769
24. Le Bars D & Villanueva L. Electrophysiological Evidence for the Activation of Descending Inhibitory Controls by Nociceptive Afferent Pathways. Prog Brain Res 1988; 77: 275-299
25. Gebhart GF. Descending Modulation of Pain. Neurosci Biobehav Rev 2004; 27: 729-737
26. Watkins LR, Milligan ED, Maier SF. Spinal Cord Glia: New Keys in Pain. Pain 2001; 93: 201-205
27. Rock RB, Gekker G, Hu S et al. Role of Microglia in Central Nervous System Infections. Clin Microbiol Rev 2004; 17: 942-964
28. Watkins LR & Maier SF. Immune Regulation of Central Nervous System Functions: From Sickness Responses to Pathological Pain. J Intern Med 2005; 257: 139-155
29. Crofford LJ. The Hypothalamic-Pituitary-Adrenal Axis in the Pathogenesis of Rheumatic Diseases. Endocrinol Metab Clin North Am 2002; 31: 1-13
30. Crofford LJ, Pillemer SR, Kalogeras KT et al. Hypothalamic-Pituitary-Adrenal Axis Perturbations in Patients with Fibromyalgia. Arthritis Rheum 1994; 37: 1583-1592
31. Griep EN, Boersma JW, Lentjes EG et al. Function of the Hypothalamic-Pituitary-Adrenal Axis in Patients with Fibromyalgia and Low Back Pain. J Rheumatol 1998; 25: 1374-1381
32. McLean SA, Williams DA, Harris RE et al. Momentary Relationship between Cortisol Secretion and Symptoms in Patients with Fibromyalgia. Arthritis Rheum 2005; 52: 3660-3665
33. Branco JC. Hypothalamic-Pituitary-Adrenal Axis Dysfunction as a Contributory Factor to Chronic Pain and Depression. Les Entretiens du Carla - Fibromyalgia: About Mechanism 2005; 8: 60-63

34. Jones KD, Deodhar P, Lorentzen A et al. Growth Hormone Perturbations in Fibromyalgia: A Review. Semin Arthritis Rheum 2007; 36: 357-362
35. El Maghraoui A, Tellal S, Achemlal L et al. Bone Turnover and Hormonal Perturbations in Patients with Fibromyalgia. Clin Exp Rheumatol 2006; 24: 428-431
36. Wolfe F, Russell IJ, Vipraio G et al. Serotonin Levels, Pain Threshold and Fibromyalgia Symptoms in the General Population. J Rheumatol 1997; 24: 555-559
37. Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal Fluid Biogenic Amine Metabolites in Fibromyalgia/Fibrositis Syndrome and Rheumatoid Arthritis. Arthritis Rheum 1992; 35: 550-556
38. Wood PB & Holman AJ. An Elephant among Us: The Role of Dopamine in the Pathophysiology of Fibromyalgia. J Rheumatol 2009; 36: 221-224
39. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread Pain in Fibromyalgia is related to a Deficit of Endogenous Pain Inhibition. Pain 2005; 114: 295-302
40. Sorensen J, Graven-Nielsen T, Henriksson KG et al. Hyperexcitability in Fibromyalgia. J Rheumatol 1998; 25: 152-155
41. Kosek E & Hansson P. Modulatory Influence on Somatosensory Perception from Vibration and Heterotopic Noxious Conditioning Stimulation in Fibromyalgic Patients and Healthy Subjects. Pain 1997; 70: 41-51
42. Vierck CJ Jr, Staud R, Price DD et al. The Effect of Maximal Exercise on Temporal Summation of Second Pain (Windup) in Patients with Fibromyalgia Syndrome. J Pain 2001; 2: 334-344
43. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia. Arthritis Rheum 2002; 46: 1333-1343
44. Desmeules JA, Cedraschi C, Rapiti E et al. Neurophysiologic Evidence for a Central Sensitization in Patients with Fibromyalgia. Arthritis Rheum 2003; 48: 1420-1429
45. Banic B, Petersen-Felix S, Andersen OK et al. Evidence for Spinal Cord Hypersensitivity in Chronic Pain after Wiplash Injury and in Fibromyalgia. Pain 2004; 107: 7-15
46. Lutz J, Jager L, de Quervain D et al. White and Gray Matter Abnormalities in the Brain of Patients with Fibromyalgia. A Diffusion-Tensor and Volumetric Imaging Study. Arthritis Rheum 2008; 58: 3960-3969
47. Cohen H, Neumann L, Shore M et al. Autonomic Dysfunction in Patients with Fibromyalgia: Application of Power Spectral Analysis of Heart Rate Variability. Semin Arthritis Rheum 2000; 29: 217-227
48. Cohen H, Neumann L, Alhosshle A et al. Abnormal Sympathovagal Balance in Men with Fibromyalgia. J Rheumatol 2001; 28: 851-859
49. Martinez-Lavin M, Leon A, Hermosillo AG et al. Circadian Studies of Autonomic Nervous Balance in Patients with Fibromyalgia: A Heart Rate Variability Analysis. Arthritis Rheum 1998; 41: 1966-1971
50. Maekawa K, Twe C, Lotaif A et al. Function of Beta-Adrenergic Receptors on Mononuclear Cells in Female Patients with Fibromyalgia. J Rheumatol 2003; 30: 364-370
51. Kadetoff D & Kosek E. The Effects of Static Muscular Contraction on Blood Pressure, Heart Rate, Pain Ratings and Pressure Pain Thresholds in Healthy Individuals and Patients with Fibromyalgia. Eur J Pain 2007; 11: 39-47
52. Branco JC, Atalaia A, Paiva T. Sleep Cycles and Alpha-Delta Sleep in Fibromyalgia Syndrome. J Rheumatol 1994; 21: 1113-1117
53. Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha Sleep Characteristics in Fibromyalgia. Arthritis Rheum 2001; 44: 222-230
54. Rizzi M, Sarzi-Puttini P, Atzeni F et al. Cyclic Alternating Pattern: A New Marker of Sleep Alteration in Patients with Fibromyalgia? J Rheumatol 2004; 31: 1193-1199
55. Gieseck T, Williams DA, Harris RE et al. Subgrouping of Fibromyalgia Patients on the Basis of Pressure Pain Thresholds and Psychological Factors. Arthritis Rheum 2003; 48: 2916-2922
56. McBeth J, Silman AJ. The Role of Psychiatric Disorders in Fibromyalgia. Curr Rheumatol Rep 2001; 3: 157-164
57. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity: A Literature Review. Arch Intern Med 2003; 163: 2433-2455
58. Clauw DJ & Crofford LJ. Chronic Widespread Pain and Fibromyalgia. What we Know and What we Need to Know. Best Pract Res Clin Rheumatol 2003; 17: 685-701
59. Giamberardino MA. Update on Fibromyalgia Syndrome. Pain Clinical Updates 2008; 16: 1-6
60. Dadabhoy D & Clauw DJ. Therapy Insight: Fibromyalgia - A Different Type of Pain Needing, a Different Type of Treatment. Nature Clin Pract Rheumatol 2006; 364-372