

# The First Israeli Fibromyalgia Congress, February 2013

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**F**ibromyalgia is a clinical disorder characterized by widespread pain, diffuse tenderness, and concomitant mood, cognitive and functional impairments [1]. Using a validated screening questionnaire, the prevalence of this syndrome in Israel is estimated to be 2.5% of the adult population. It is significantly more common in women, four to fivefold depending on the assessment tool and criteria used [2,3].

Given the high prevalence of fibromyalgia in the general population worldwide as well as Israel, and the local medical community's increasing interest in this entity, the first Israeli fibromyalgia conference was convened on 15 February at the Peres Peace Center in Jaffa-Tel Aviv. The meeting was attended by 200 rheumatologists, pain specialists and primary care physicians, united in their wish to understand the epidemiological, pathogenetic, genetic and therapeutic aspects of this syndrome.

Dr. Dan Buskila from the Soroka Medical Center, Beer Sheva, elaborated on the unraveling genetic background of fibromyalgia. Recent evidence suggests that genetic factors may play a role in its pathogenesis in combination with various environmental stimuli. Evidence for the role of genetics in development of this syndrome comes from studies demonstrating familial aggregation and the recognition that specific genes might confer an increased risk

of an individual developing fibromyalgia [4-6]. Evidence suggests a role for polymorphisms of genes in the serotonergic, dopaminergic and catecholaminergic systems in the pathogenesis of fibromyalgia and related conditions. Environmental factors may trigger the development of these disorders in genetically predisposed individuals. These polymorphisms are not specific for fibromyalgia and are associated with other chronic pain syndromes, affective disorders and functional somatic conditions. The mode of inheritance is unknown, but it seems to be most probably polygenic. Recognition of these gene polymorphisms may help to subgroup fibromyalgia patients and to devise treatment according to an appropriate and logical pharmacologic approach. More robust studies with a larger number of patients and well-matched controls are needed to better clarify the role of genetic factors in fibromyalgia and related conditions. Newer genetic methodologies including haplotype analysis, gene expression studies and proteomics should be applied in future studies.

Dr. Howard Amital from the Sheba Medical Center discussed the environmental aspects that often perpetuate the manifestations of the syndrome. A history of negative life events is often described by patients with fibromyalgia. Increased rates of physical, psychological and sexual trauma are frequently encountered in these patients [7-9]. Many patients, unfortunately, face hostility from social workers and medical caregivers which is often provoked by their withdrawing behavioral patterns. However, it is not entirely clear whether the psychological disturbances associated with the fibromyalgia construct

are the result of chronic illness and pain or whether they play a role in their cause.

Typical physical injuries were found to be more prevalent and clearly related to the syndrome. Buskila et al. [10] reported that 21.6% of patients with whiplash road accident injuries developed fibromyalgia within 3 months in contrast to 1.7% of control patients with fractures in the lower extremities. After 3 years, 60% of patients who developed fibromyalgia continued to suffer from its manifestations. Interestingly, the symptoms persisted in women, whereas men had a much more favorable outcome [11].

Cohen and team [8] demonstrated that more than 50% of 77 patients (40 women and 37 men) with fibromyalgia had clinically significant levels of post-traumatic stress disorder. Women with fibromyalgia and PTSD reported a greater number of post-traumatic events than did male patients. These results were further investigated by Amital et al. [7], who reported a high prevalence of fibromyalgia (49%) among men with combat-related PTSD. It was also shown that these comorbidities potentiated each other, thus subjects with debilitating PTSD also suffered from a more severe form of fibromyalgia [7].

Other investigators observed that women with fibromyalgia who experienced sexual abuse reported significantly more symptoms than did non-sexually abused women [12]. Dobie and co-authors [13] elaborated on the growing population of traumatized female military veterans. Of 1259 women who completed their survey, 266 had PTSD. Of these, almost half expe-

PTSD = post-traumatic stress disorder

rienced premenstrual symptoms compared to approximately 25% of non-traumatized female veterans. In their study, fibromyalgia was detected three times more often in females with PTSD compared to those without PTSD.

We also demonstrated a strong association between women with premenstrual dysphoric syndrome and fibromyalgia. These women scored significantly higher in the measures of pain and tenderness as well as in severity of premenstrual symptoms compared to controls [14]. This finding reinforced previous reports suggesting an association between PTSD and fibromyalgia [15]. Various medical conditions often facilitate the emergence of pain syndromes; moreover, several reports have underlined the impact of emotions and stressful events on the pathogenesis of fibromyalgia. In addition, particularly with chronic medical conditions, exhaustion deriving from resilience and defense mechanisms is often associated with enhanced pain sensation [3]. We believe that this might elucidate the high frequency of pain syndromes among subjects who experience chronic as well as acute traumatic physical or mental events such as malignancies or terror attacks [16-18].

There is also much speculation on triggering factors or associated disorders that may contribute to the fibromyalgia syndrome. Some studies show that infections such as hepatitis B virus, hepatitis C virus, human immunodeficiency virus and Lyme disease played a role in the induction of fibromyalgia in these patients [19].

Dr. Jacob Ablin presented the new Israeli guidelines for the diagnosis and treatment of fibromyalgia and focused on the pharmacological aspects of treatment. The purpose of the Israeli guideline project is to develop practical and evidence-based recommendations for the Israeli health care system. A panel of physicians with clinical and research experience in the field of fibromyalgia, under the auspices of the Israeli Rheumatology Association, conducted a systematic review of the current literature regarding the diagnosis and treatment of the disorder. Using an iterative discussion

procedure, recommendations were reached and expert opinion was introduced where evidence was considered incomplete. The literature was searched on Medline using the terms “Fibromyalgia” and “Treatment guidelines” with no limitation on years of publication. In addition, a focused search in the Cochrane Collaboration database at <http://www.cochrane.org/> revealed relevant review articles and meta-analyses. The group has developed guidelines relating to both the diagnosis and the treatment of the syndrome. Typically, fibromyalgia is diagnosed in individuals complaining of widespread musculoskeletal in whom other pain disorders have been excluded. Nonetheless, it must be stressed that fibromyalgia may develop in coexistence with other disorders. Hence, the medical history must be searched for other diagnoses that may explain the development of widespread pain. Currently there is no specific diagnostic laboratory test for the diagnosis of fibromyalgia. The diagnosis remains basically clinical, and the purpose of the lab workup is to rule out alternative diagnoses. Nonetheless, the following list of tests is recommended in all cases before arriving at a definitive diagnosis of fibromyalgia: complete blood count, renal function tests (creatinine and urea), serum calcium and phosphorous levels, liver function tests, creatine phosphokinase, erythrocyte sedimentation rate, C-reactive protein, thyroid-stimulating hormone, and vitamin D. The decision whether to perform serological tests including antinuclear antibodies and rheumatoid factor depends on the presence of clinical hints and is left to the discretion of the attending physician.

Educating patients and family on the nature of fibromyalgia is an important part of the initial management. Emphasis should be laid on explaining the non-progressive nature of the entity while acknowledging its frequently chronic nature.

Treatment usually calls for a multimodal strategy incorporating pharmacological and non-pharmacological aspects. Graded exercise is essential. Other non-pharmacological treatments such as cog-

nitive behavioral therapy, hydrotherapy and meditative movement treatments (Tai chi, yoga, etc.) are supported to various degrees by the evidence and have a role in the therapeutic plan.

Pharmacological treatment should always start at low doses and increase gradually. Medication with an effect on central nervous system processing of pain may alleviate symptoms of pain and improve sleep. A personalized strategy of treatment is always required. Specific medications in common use include the tricyclic antidepressants such as serotonin-norepinephrine reuptake inhibitors and anticonvulsants (e.g., pregabalin). Non-steroidal anti-inflammatory drugs, opioids, steroids and benzodiazepines are usually not recommended. A stratified approach was outlined.

Dr. Aloush discussed the non-pharmacological treatments and underlined the need for a dual approach, addressing not only the pain and fatigue but also their functional consequences: social and personal isolation, decreased activity, stress, and maladaptive illness behaviors. The comprehensive treatment of pain requires a biopsychosocial assessment including evaluation of comorbidities, affective vulnerability, beliefs and attitudes, as well as social and familial factors. Hence, the optimal treatment strategy calls for a multidisciplinary approach based on physical, cognitive, behavioral and educational elements.

Aerobic exercise is critical and leads to the reduction of pain, fatigue and depressed mood. It also improves quality of life and physical fitness. Mild-to-moderate intensity exercise, such as walking, cycling or dancing, two to three times a week for at least 4 to 6 weeks, is necessary for symptom relief. It is mandatory to limit the exercise level to the patient's starting capability. Similarly, hydrotherapy is strongly recommended. Cognitive behavioral therapy is used to modify dysfunctional thoughts that can exacerbate and perpetuate pain, suffering and diminished functioning, as well as to change behavior and reduce health care-seeking behavior. Meditative

movement therapies such as Tai chi and yoga may help to alleviate pain, fatigue and depression, thereby improving quality of life and sleep.

Dr. Ronny Vered, a family physician, presented a practical approach to the diagnosis of fibromyalgia. Dr. Vered discussed the tests that should and should not be routinely ordered in the workup of patients suspected of suffering from fibromyalgia, as well as cases where referral to a specialist might be useful. He described the use of the Fibromyalgia Rapid Screening Test (FiRST) as a screening tool for diagnosing fibromyalgia at the primary care level. Dr. Vered stressed that family physicians are often the first to encounter fibromyalgia patients and thus diagnosis and recognition are pertinent.

The guest speaker at the symposium was Prof. Winfried Hauser, specialist in psychosomatic medicine at the Interdisciplinary Center for Pain Medicine in Saarbrücken, Germany. Dr. Hauser presented some current controversies related to the syndrome. Should it be considered a somatic or a mental disease? Should tender points be used or abandoned? What types of treatment are currently recommended and what types should be discouraged? And what does the future hold for the management of fibromyalgia?

Previous nomenclature (ICD-10) adopted the term “Persistent somatoform pain disorder,” defined as “...at least 6 months, continuously, on most days, severe and distressing pain, in any part of the body, which cannot be explained adequately by evidence of a physiological process or a physical disorder and occurs in association with emotional conflicts or psychosocial problems.” While many fibromyalgia patients refuse to accept a psychosocial explanation for their symptoms, Hauser et al. [20] demonstrated that the spread of pain or increase in pain intensity is associated with emotional conflict or psychosocial problems in 60%–80% of fibromyalgia patients. The ICD-11 has abolished the term “Somatoform disorder” and created a new term – “Bodily distress syndrome.” The upcoming DSM-V has also abolished “Somatoform disorder,” creating

“Physical symptom disorder” instead. Dr. Hauser presented the case for describing fibromyalgia as a “functional somatic syndrome.” Based on the definition of Mayou et al. [21], this term describes conditions characterized by a typical cluster of chronic symptoms, together with exclusion of somatic disease that could sufficiently explain such symptoms. Other examples of functional somatic syndromes include tension headache, temporomandibular joint disorder, non-cardiac chest pain, functional dyspepsia, etc. Discussing the relationship between fibromyalgia and depression, Dr. Hauser stressed that although the prevalence of depressive symptoms in fibromyalgia patients has been estimated at 20% to 80% and the prevalence of fibromyalgia among depression patients between 20 and 30%, it is incorrect to describe fibromyalgia as an affective spectrum (depressive) disorder. Mutual genetic and environmental factors, as well as similar triggers, appear however to be involved in the pathogenesis of both disorders. Dr. Hauser addressed the issue of the use of tender points for the diagnosis of fibromyalgia, arguing that while they serve a role in pain assessment in primary care they are no longer necessary for performing a proper diagnosis. Unlike the original 1990 American College of Rheumatology classification criteria for the fibromyalgia syndrome, the new proposed diagnostic criteria incorporate a broader range of symptoms besides pain and tenderness alone and may also be used as a severity scale [22,23]. Regarding treatment, Dr. Hauser endorsed the strong recommendation for non-pharmacological modalities that are evidence based: aerobic exercise (low intensity), relaxation training, cognitive behavioral therapy, low intensity strength training, and meditative movement therapies (Qigong, Tai chi, yoga). He reviewed the medications that have achieved a high ranking level of evidence according to the German guidelines for the management of fibromyalgia. Strong evidence was assigned to pregabalin, duloxetine, milnacipran and sodium oxybate, moderate evidence to amitriptyline and low evidence to many others including

selective serotonin re-uptake inhibitors and tramadol.

In conclusion, future trends in the management of fibromyalgia may include new medications, incorporation of telephone-based psychological therapies, tailored treatment and multi-component treatment.

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## Capsule

### CD28 and ITK signals regulate autoreactive T cell trafficking

Activation of self-reactive T cells and their trafficking to target tissues leads to autoimmune organ destruction. Mice lacking the co-inhibitory receptor cytotoxic T lymphocyte antigen 4 (CTLA-4) develop fatal autoimmunity characterized by lymphocytic infiltration into non-lymphoid tissues. Jain et al. demonstrate that the CD28 co-stimulatory pathway regulates the trafficking of self-reactive *Ctla4*<sup>-/-</sup> T cells to tissues. Concurrent ablation of the CD28-activated Tec family kinase ITK does not block spontaneous T cell activation but instead causes self-reactive *Ctla4*<sup>-/-</sup> T cells to accumulate in secondary lymphoid organs. Despite excessive spontaneous

T cell activation and proliferation in lymphoid organs, *Itk*<sup>-/-</sup>; *Ctla4*<sup>-/-</sup> mice are otherwise healthy, mount antiviral immune responses, and exhibit a long lifespan. The authors propose that ITK specifically licenses autoreactive T cells to enter tissues to mount destructive immune responses. Notably, ITK inhibitors mimic the null mutant phenotype and also prevent pancreatic islet infiltration by diabetogenic T cells in mouse models of type 1 diabetes, highlighting their potential utility for the treatment of human autoimmune disorders.

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## Capsule

### HIV1 evades innate immune recognition through specific cofactor recruitment

Human immunodeficiency virus (HIV)-1 is able to replicate in primary human macrophages without stimulating innate immunity despite reverse transcription of genomic RNA into double-stranded DNA, an activity that might be expected to trigger innate pattern recognition receptors. Rasaiyaah et al. reasoned that if correctly orchestrated HIV-1 uncoating and nuclear entry is important for evasion of innate sensors, then manipulation of specific interactions between HIV-1 capsid and host factors that putatively regulate these processes should trigger pattern recognition receptors and stimulate type 1 interferon (IFN) secretion. The authors show that HIV-1 capsid mutants N74D and P90A, which are impaired for interaction with cofactors cleavage and polyadenylation specificity factor subunit 6 (CPSF6) and cyclophilins (Nup358 and CypA), respectively, cannot replicate in primary human monocyte-derived macrophages because they trigger innate sensors leading to nuclear translocation of NF- $\kappa$ B and IRF3, the production of soluble type 1 IFN and induction of an

antiviral state. Depletion of CPSF6 with short hairpin RNA expression allows wild-type virus to trigger innate sensors and IFN production. In each case, suppressed replication is rescued by IFN-receptor blockade, demonstrating a role for IFN in restriction. IFN production is dependent on viral reverse transcription but not integration, indicating that a viral reverse transcription product comprises the HIV-1 pathogen-associated molecular pattern. Finally, they show that they can pharmacologically induce wild-type HIV-1 infection to stimulate IFN secretion and an antiviral state using a non-immunosuppressive cyclosporine analogue. The authors conclude that HIV-1 has evolved to use CPSF6 and cyclophilins to cloak its replication, allowing evasion of innate immune sensors and induction of a cell-autonomous innate immune response in primary human macrophages.

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