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Congress Chairs

Jacob Ablin
Tel-Aviv Sourasky Medical Center, Israel

Piercarlo Sarzi-Puttini
L. Sacco University Hospital, Milan, Italy

Abstracts

IS-01

UPDATE ON FIBROMYALGIA DIAGNOSTIC CRITERIA, CLASSIFICATION, DIFFERENTIAL DIAGNOSIS...

Piercarlo Sarzi-Puttini, Valeria Giorgi
Rheumatology Unit, ASST-Fatebenefratelli L. Sacco University Hospital, Milan, Italy.

Even if physicians started to recognize fibromyalgia as a clinical entity decades ago (1), it endures to be a controversial disease, even regarding its nosological classification. Diagnostic complexity is increased by the fact that it is characterized by a complex polysymptomatology, which can continuously evolve during the course of the disease in each single patient (2). Therefore, diagnostic and classification criteria are still developing.

The American College of Rheumatology criteria was the first to put some order in fibromyalgia diagnosis. In the 90s it was shortly been officially recognized as a discrete clinical entity; therefore, physicians needed to have a clear, exhaustive list of symptoms that could be present in these types of patients (ACR 2010 symptom severity scale (3) is a clear example). Although comprehensive, these criteria were not very feasible in daily clinical practice. They started to be simplified in 2011 (4), shortening the list of associated symptoms, and afterwards in 2016 (5), emphasizing more the concept of "generalized pain". Anyway, latest AAPT diagnostic criteria (6) tried to create a really feasible tool for physicians in order to facilitate fibromyalgia diagnosis. They divided the criteria in different dimensions. Dimension 1 includes core diagnostic criteria, which are three: 1) multisite pain defined as 6 or more pain sites from a total of 9 possible sites; 2) Moderate to severe sleep problems OR fatigue; 3) MSP plus fatigue or sleep problems must have been present for at least 3 months. Other dimensions can reinforce diagnostic conviction: common features, epidemiology, psychiatric comorbidities, functional consequences and risk factors can all be taken into account by the physicians and have all to be thoroughly investigated during the history taking.

Importantly, AAPT criteria emphasised the fact that the presence of other disorders does not exclude the existence of fibromyalgia as a comorbidity; in fact, many rheumatic diseases have a high prevalence in fibromyalgia population – the opposite also being true. However, there may be a significant reluctance to diagnose fibromyalgia by some physicians, because of a number of reasons (7): uncertainty about diagnosis, especially in the lack of specific biomarkers or pathognomonic signs, hesitancy in "labelling" a patient with a "stigmatizing" syndrome, and so on.

In contrast, in some cases other conditions can mimic fibromyalgia, mainly: rheumatic diseases of recent onset (polymyalgia rheumatica, rheumatoid arthritis, etc.), endocrine diseases (hypothyroidism, vitamin D deficiency), gastrointestinal diseases (celiac disease), infectious diseases (Lyme disease, hepatitis C) and the early stages of a malignancy such as metastatic cancer, leukemia and lymphoma (8). Specific laboratory tests and a thorough history taking should always be performed.

Finally, it is getting clearer that, even though diagnostic criteria are quite accurate in delineating the typical symptomatic profile of fibromyalgia patients, people suffering from fibromyalgia are actually divided into sub-populations on the basis of their main symptoms and of their symptoms progression (9, 10). In particular, it is important to separate those patients whose main complaint is pain from those patients who have a prominent mood disorder component of their disease (mainly anxiety and depression). The creation of these, still hypothetical, patient subgroups in daily clinical practice would be of extreme utility from a therapeutic perspective.

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IS-02

UPDATE ON FIBROMYALGIA TREATMENT AND GUIDELINES

Jacob Ablin
Tel-Aviv Sourasky Medical Center, Israel.

While increasing knowledge is accumulating regarding the pathogenesis and underlying neurological pathways of the fibromyalgia Syndrome (FMS) and other centralized pain disorders, this progress has yet to be associated with major breakthroughs in the therapeutic realm. Treating FMS remains a complex and all-too-often frustrating endeavor. While there is evidence indicating that some patients significantly improve, or even cease to fulfill diagnostic criteria of FMS, many patients continue to experience a chronic course with ups and downs and fail to achieve any dramatic improvement after starting treatment. Moreover, while the introduction of three FDA – approved medications, *i.e.* Pregabalin, Duloxetine and Milnacipran during the first decade of the century, appeared to usher in a new era in the pharmacological treatment of FMS, these three have not been followed by any additional drug - approvals and evidence has since shown that only a relatively small proportion of patients are significantly improved with these treatments as well. This reality has led to an increasing emphasis on the necessity of implementing a multidisciplinary approach, combining pharmacological with non – pharmacological tools and recruiting the participation of healthcare professionals from various areas, *e.g.* psychotherapists, physiotherapists etc. as recognized by current treatment guidelines such as the 2012 Canadian, (1) German (2) and the EULAR 2016 guidelines (3). Exercise has been recognized as one of the most evidence-based modalities for treating FMS with the highest level of recommendation. Additional non-pharmacological interventions include cognitive behavioral treatment (CBT), movement meditative therapies, hydrotherapy etc.

Among pharmacological treatments, amitriptyline is still often used as first line therapy and has received a strong recommendation from some of the guidelines. Anticonvulsants, which mainly include Pregabalin and gabapentin, are still used with varying rates of success although their use is often limited by side effects. The Serotonin – Norepinephrine reuptake inhibitors (SNRIs), Duloxetine and Milnacipran, also receive mixed – recommendations by various guidelines and appear to have a role in specific patients. Cyclobenzaprine, a centrally acting muscle - relaxant, is recommended by the EULAR (weak for). Selective serotonin reuptake inhibitors (SSRI) are not recommended by EULAR but are recommended by German and Canadian guidelines. In real life, combining SSRIs with amitriptyline is often a practical option, since many patients may present already being treated with SSRI (for depression or anxiety) and adding amitriptyline may be easier than switching to a SNRI under such circumstances.

Strong opioids are generally not recommended for use in fibromyalgia and there are indications that their use may in fact be deleterious, due to exacerbating opioid - induced hyperalgesia. Tramadol, a weak opioid with additional 5-HT and norepinephrine reuptake inhibition activity, does show some efficacy in FMS and is recommended by EULAR and Canadian guidelines. Cannabinoids continue to receive a great deal of attention in the field of FMS, as well as chronic pain in general. There is both theoretical as well as multiple anecdotal indications supporting the use of cannabinoids in the treatment of FMS for both improving sleep as well as combating pain, although this form of treatment cannot be regarded as evidence - base at present and most guidelines remain guarded on the question. Moreover, there is currently no consensus regarding the question which cannabinoid or cannabinoids is optimal for FMS, *i.e.* THC, CBD, an "entourage" of cannabinoids etc. There is an obvious need for further research on this topic.

In view of the limited success rates of pharmacological interventions, there is growing interest in the prospect of achieving neuroplasticity and reducing central sensitization in FMS, through various techniques. Among the more established of these, one might mention Trans cranial magnetic stimulation (TMS) and Trans cranial direct current stimulation (tDCS), while more experimental approaches include the implementation of hyperbaric oxygen therapy (HBOT) and neuro-feedback. Interesting results have been achieved with these last two modalities and research is ongoing. At present however these modalities remain investigational in nature and are not included in current management guidelines.

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IS-03

IS THERE ANYTHING NEW AROUND THE CORNER?

Valerie Aloush, MD
Rheumatology Institute, Tel Aviv Sourasky Medical Center and Sackler Medical School, Tel Aviv University, Israel.

For years considered an unexplained disorder, with controversies about its definition, causes, management, and even its existence, fibromyalgia has evolved in recent years into an impressive field of research and progress; this evolution has been associated with better understanding of pathophysiology as well as increasing recognition and awareness regarding this highly prevalent syndrome among both health care professionals and society at large.

Diagnostic criteria have considerably changed during the last decade, attempting to integrate new clinical and pathophysiological insights, better define generalized pain, emphasized the presence of associated symptoms and recognize the validity of making a diagnosis of fibromyalgia as a potential comorbid entity, rather than defining the syndrome by exclusion. Last year, an international fibromyalgia working group on behalf of the American Pain Society published a new set of diagnostic criteria, incorporating the core symptoms of fibromyalgia, associated features, common medical and psychiatric comorbidities, psychosocial and functional consequences, as well as pathophysiology, enabling better diagnosis and classification of fibromyalgia among other chronic pain syndromes.

Research in the field of pathophysiology has expanded considerably, exploring the role of genetics, immune system, autonomic system, gut microbiome, inflammatory response, neurotransmitters, psychological factors and life events, leading to a better and more holistic comprehension of fibromyalgia. Recognition of fibromyalgia as a comorbid disorder, especially along with other rheumatic diseases, with its implications on evaluation, disease activity scores, treatment and outcomes, is crucial to improve management of these diseases. On the other hand, specifically addressing psychiatric comorbidities with psychological therapies will also permit a decrease in the burden of somatic symptoms and physical distress.

New therapeutic options are also emerging, in order to mitigate the aberrant patterns of central pain processing demonstrated in fibromyalgia, alleviate symptoms and improve functioning. Neuromodulation by transcranial magnetic stimulation or neurofeedback are promising strategies, and further research will help in defining the optimal stimulation protocol and the most effective brain targets. Recent studies have shown symptomatic improvement in fibromyalgia patients treated by hyperbaric oxygen therapy (HBOT). Better understanding the effects of HBOT on brain activity and the mechanisms underlying such effects, as well as defining clinical/psychological settings responsive to this therapy, will help identify patients likely to improve with HBOT.

Finally yet importantly, despite considerable uncertainty regarding mechanisms of action and its exact role in the management of pain and non-pain symptoms in fibromyalgia, medical cannabis has become in the last years a focus of intense research and controversies, but also a source of hope for patients.

Understanding and treating fibromyalgia is still challenging, but the future definitely lies in an integrative approach, taking into account all we are still learning in terms of genetic background, psychosocial factors, comorbidities, neurotransmitter profile and neuroimaging pain signature in order to define the optimal individualized patient profile and in order to devise the necessary elaborate, unique, personalized treatment approach.

IS-04

FUNCTIONAL OR DYSFUNCTIONAL SYNDROMES: IS THIS THE PROBLEM?

Roberto Casale, MD PhD
Opusmedica, PC&R Patient, Care & Research Network, Piacenza, Italy.

The list of physiopathological mechanisms attributed to what is now recognized under the name of fibromyalgia is more or less long as it is that of Complex Regional Pain Syndromes (CRPS). For both of them a possible direct participation of a lesion or a disease of the nervous system in their genesis has been recognized: CRPS Type II and for fibromyalgia the presence of a C-fiber neuropathy (small fiber polyneuropathy). This has been induced someone to hypnotize that fibromyalgia is a form of CRPS.

None of these pathological findings have been recognized as the distinctive landmark of the disease. Moreover, and possibly at the very bottom of the problem, there is the difficulty in assigning fibromyalgia to the field of neuropathic pain or in the opposite field of nociceptive pain in the absurd attempt to distinguish between what is the nervous system from what is not. It is worth of mention to cite what is the actual definition of nociceptive pain. The term is used to describe pain occurring with a normally functioning somatosensory nervous system to contrast with the abnormal function seen in neuropathic pain. However, this definition does not clearly distinguish between acute and chronic pain and moreover what is defined as neurogenic inflammation. Neurogenic inflammation is the best example of overlapping mechanisms: a pathological condition outside the nervous system sustained by the same nervous system that at a certain point changes its toning, becoming more reactive and sometime triggering a self -maintaining process. Indeed scientific literature is full of papers related to the strong possibility that many if not all types of pain have some common mechanisms and that we have to deal with the ability to the nervous system -but I must say, the human body- in some circumstances to react and to adapt to inner and outer stimuli of sufficient bio-psycho-social importance. In this context fibromyalgia in its full clinical feature is the end of this process. This ability has been defined by biologists as plasticity: all cells are plastic from skin cells to more specialized cells like those of the nervous system, both sharing the same embryologic origin. Plasticity as all the biological dynamic systems can varies in term of hypo- or hyper-functioning. An interesting case is that of the modification in the thickness of some brain cortex areas after prolonged torture: firstly the somatosensory areas seem to overreact while later the same areas shrink. This is paralleled in fibromyalgia where different cortical areas seem to be overactive while others are hypoactive producing an overall maladaptive situation. This term has been proposed by Clifford Woolf (3) as maladaptive plasticity and fibromyalgia may represents a peculiar case of maladaptive plasticity where hypo-and hyper-functioning areas are present in the brain.

Recently to try to fill the conceptual nonsense of non-nociceptive non-neuropathic chronic pains a new term has been coined: nocipastic pain to define all those pains that are neither nociceptive nor neuropathic, including fibromyalgia (2). A part from the recognized inadequacy of the formulation of the definition (1), nocipastic pain may by applicable for some pathologies still in the taxonomy limbo. However it doesn't seem to be applicable to fibromyalgia if we take into account the bio-psicho-social model to understand the natural history of the fibromyalgic patient where, in a quite relevant number of cases, the trigger toward the evolution toward fibromyalgia has to be found in some psycho-social causes and where no apparent biological alterations are present in the nervous system.

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IS-05

CONCOMITANT FIBROMYALGIA IN RHEUMATIC DISEASES

Ori Elkayam, MD
Department of Rheumatology, Tel Aviv Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Israel.

Fibromyalgia is characterized by widespread pain accompanied by somatic symptoms such as fatigue and sleep disorders. The diagnostic criteria for fibromyalgia have undergone many changes over the years. The first criteria of the American college of rheumatology (ACR) emphasized the presence of tender points. These criteria were changed in 2010 with an emphasis on the presence of pain along with somatic symptoms and the negation of another joint disease explaining patients pain .In 2016, the criteria were revised removing the negative criterion for another rheumatic disease. This change is required in light of the fact that fibromyalgia is particularly prominent in patients with rheumatic diseases. In addition, it is of great importance to recognize fibromyalgia as a source of pain and to separate it from the inflammatory process in order to properly treat the patient and prevent unnecessary changes of treatment. Databases indicate greater switching of biologics among patients with inflammatory arthropathies and concomitant fibromyalgia.

It is estimated that fibromyalgia is present in about 20 to 30% of patients with rheumatic diseases. A North American database of approximately 6000 patients identified a 21% prevalence of fibromyalgia in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and osteoarthritis. Similar rates have been described in spondyloarthritis (SpA), including psoriatic arthritis (PsA) and other connective tissue diseases. It should be noted that, like in primary fibromyalgia, secondary fibromyalgia is more common in women.

Different studies have shown that the intensity of pain and disability is higher in patients with rheumatic disease such as RA and PsA and concomitant fibromyalgia. This fact may a have a profound impact on the evaluation of disease activity in patients with inflammatory rheumatic diseases

The treatment of RA and SpA is based on the treat to target concept. In the last 2 decades, the treatment of these diseases has been revolutionized by the introduction of biologic agents. The treat to target strategy aims at reaching a state of remission or low disease activity. When evaluating RA, common measures of disease activity are Disease activity score-28 (DAS-28) or Simplified disease activity score (SDAI). Both measures include the number of swollen and tender joints out of 28, patient's disease activity assessment and a measure of inflammation such as ESR or CRP. Assessment of the disease activity by the patient may be influenced by many factors such as the objective state of inflammation but also by the intensity of non- inflammatory pain, due to fibromyalgia. It has been unequivocally shown that the presence of fibromyalgia among RA and PsA patients significantly increases the various measures of disease activity. A patient with RA and fibromyalgia may demonstrate a lack of swollen joints along with multiple tender joints raising the levels of DAS to rates of moderate to high disease activity. The same has been shown in PsA where the difficulty is further increased by the presence of enthesitis which may be confounded by tender points.

In patients with inflammatory disease and concomitant fibromyalgia, it seems that any change in disease modifying drugs (DMARDS) should be based on more objective methods of evaluation such as ultrasound and not only rely on physical examination and patients reported outcomes.

In conclusion, fibromyalgia is common among patients with rheumatic diseases. Identifying the phenomenon is of great importance in order to prevent misinterpretation of disease activity measures leading to unnecessary treatment. Proper identification of fibromyalgia in rheumatic patients will lead to a better understanding of patient's symptoms and appropriate treatment.

IS-06

IMPLICATIONS FOR TREATMENT, DISEASE SEVERITY ASSESSMENT AND RESEARCH

Banfi Giuseppe[1], Valeria Giorgi[2]
[1]IRCCS Istituto Ortopedico Galeazzi and Vita-Salute San Raffaele University, Italy;
[2]Rheumatology Unit, ASST-Fatebenefratelli L. Sacco University Hospital, Milan, Italy.

Disease severity assessment is an indispensable tool for every rheumatologist dealing with his or her patients. Indeed, it gives a snapshot of the current clinical situation of each patient, helping in the decision making about treatment, which could be more or less aggressive, depending on the disease severity scale; also, it allows to obtain a full picture of each patient's clinical progression in time, permitting the creation of a strong and reliable system of follow-up. The disease severity assessment should be based on reliable, easy-to-perform standard measurements of meaningful clinical outcomes. A clear example in rheumatology can be represented by the DAS28 in rheumatoid arthritis. However, it is not possible to rely on a single symptom assessment in the case of fibromyalgia, as, for example, pain intensity, since it is a syndrome comprising too many clinical aspects. Therefore, various composite indeces were validated, encompassing the main features of this polysymptomatic disease, namely pain, fatigue, sleep alteration, neurocognitive disorders, anxiety and depression. The most widely used include the Fibromyalgia Impact Questionnaire (FIQ) and its revised version (FIQR), the Fibromyalgia Assessment Status (FAS), the Fibromyalgia Survey Criteria (FSC) and the Patient Health Questionnaire 15 (PHQ15). Notwithstanding, controversies are still open regarding the reliability and usefulness of these composite tests from an inter-individual perspective, *i.e.*, consensual severity cut-off points have not been established yet, and this creates difficulties regarding not only therapeutic decision-making, but also invalidity recognition by healthcare authorities. Anyway, research is currently ongoing (1).

Disease severity assessment tools are useful, but therapeutic targets should always be set in agreement with each individual patient, in a shared decision-making process. In general, the improvement of everyday function, rather than the improvement of specific symptoms, could be considered a feasible therapeutic goal. From this perspective, treatment should be strictly individualized, combining both pharmacological and non-pharmacological tools, based on each patient's needs and symptomatology. In fact, the latest EULAR criteria (2) established a "strong" recommendation only for exercise and fitness for fibromyalgia patients. In order to give general indications for physicians' daily clinical practice, we can divide the treatment in 3 "pillars": 1) Education and fitness; 2) Pharmacological treatment; 3) Psychotherapy. It is advisable to start each therapeutic plan with an element taken from each single pillar, in order to be effective in all symptomatologic domains.

New promising treatment tools are currently under investigation. From a pharmacological point of view, mirtazapine, an α2 adrenergic antagonist with serotonergic and noradrenergic effects, and milnacipran, a serotonin and norepinephrine reuptake inhibitor, were tested for their effectiveness in fibromyalgia, but results have so far been controversia (3, 4). Conversely, cannabis plant seems to be a promising tool to fight fibromyalgia chronic pain (5, 6), even though further studies are needed in order to assess the correct posology and THC/CBD ratio. On the other hand, nonpharmacological treatments that are being studied include the hyperbaric oxygen therapy (7, 8) and neurostimulation (9), which, interestingly, are both able to act on neuroplasticity, which is particularly important in a disease such as fibromyalgia.

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IS-07

IMMUNE SYSTEM INVOLVEMENT IN THE DEVELOPMENT AND MANIFESTATIONS OF FIBROMYALGIA

Dror Mevorach, MD
Rheumatology Research Center, Department of Medicine, The Wohl Institute for Translational Medicine, Hadassah and the Hebrew University Medical Center and Medical School, Jerusalem, Israel.

Even though fibromyalgia is not considered by most researchers as an autoimmune or autoinflammatory disease, fibromyalgia is common in these patients, hence, the immune system involvement is plausible both as a trigger factor and /or as facilitating/preventing its manifestations and their strength. Furthermore, viruses and other infectious agents seem to be able to induce fibromyalgia, even if a direct causal relationship is not well documented. An important role dealing with these associations might be played by innate immunity, cytokines/chemokines/ growth factors, microbiome, and by glial cells, which for example, express receptors for bacteria and viruses.

Pain in rheumatologic conditions cannot always be directly correlated with frank inflammation (*e.g.* synovitis) and treatment with potent biologic agents that control inflammation does not always control pain although besides synovial pressure relief possible overlap between inflammatory pathways and pain pathways, as for example the role of the JAK system in both inflammation and chronic pain.

Fatigue is another prominent feature of these conditions, which again tends to respond only partially to potent biologic agents.

Centralized pain syndromes are associated with changes within the central nervous system that amplify peripheral input and/or generate the perception of pain in the absence of a noxious stimulus. Examples of idiopathic functional disorders that are often categorized as centralized pain syndromes include fibromyalgia, chronic pelvic pain syndromes, and even migraines. Patients often suffer from widespread pain, associated with more than one specific syndrome, and report fatigue, mood and sleep disturbances, and poor quality of life. In general, abnormal regulation and output of the hypothalamic-pituitary-adrenal axis, the "primary" stress response system, was suggested to be associated with centralized pain disorders. Activation of this axis was suggested to result in downstream production of cortisol and a dampening of the immune response. We would like to challenge this dogma, and present evidence indicating that the immune response is not a response which is subsequent to hypothalamic-pituitary-adrenal axis activation, but rather evolves simultaneously, leading perhaps to sensitization of nearby nociceptive afferents and increased peripheral input via nociceptor activation. This in turn may lead to further central sensitization, through long-term potentiation in the central nervous system.

IS-08

THE MICROBIOME AND FIBROMYALGIA: THE GUT-BRAIN AXIS

A Minerbi[1], M Fitzcharles[2]
[1]*Institute for Pain Medicine, Rambam Health Campus, Haifa, Israel;*
[2]*McGill University, Montreal Canada,*

Almost every patient with fibromyalgia (FM) asks the question whether diet may affect symptoms of FM. Furthermore, abdominal complaints consistent with irritable bowel syndrome are common in FM. The emerging understanding of the gut microbiome in both health and disease may hold pertinence for FM.

The human body exists in a complex and dynamic ecosystem with extensive microbial colonization of the gut and other tissues. This symbiosis influences health status and can be affected by environmental and genetic factors, and is a driver for metabolic and immune physiology, but alternately can play a role in pathology. The physiological effects of the gut-brain axis in both health and disease result in a bidirectional interplay between the gut (hormonal mechanisms and microbiome) and the nervous system. Neurological effects mediated via the autonomic nervous system as well as the

hypothalamic pituitary adrenal axis are directed to intestinal functional effector cells, which in turn are under the influence of the gut microbiota. Gut bacteria, in turn, have been shown to affect the activity of central-nervous-system functions, with several putative mechanisms, including, but not limited to the secretion of short-chain fatty acids, bile acids, neurotransmitters and other biologically active metabolites. Perturbations of the microbiome have been associated with a wide variety of pathologies, including the metabolic syndrome, gut related disorders, mental health conditions, immunologically mediated diseases, and with increasing evidence for effect in pain conditions. Pathological states may occur when there are perturbations of the microbiome composition, leading to alteration in its metabolic function and its interactions with the host physiology.

Any assessment of the microbiome requires meticulous attention to factors known to influence composition, including diet, age, physical activity, medications and other factors. The composition of the microbiome is typically evaluated by DNA sequencing of either bacterial specific sequences, such as 16S rRNA or by metagenomic sequencing. The function of the microbiome can be inferred by transcriptomic, proteomic and metabolomic analyses. Machine learning algorithms are used to identify specific microbiome-related patterns that distinguish patients from healthy controls.

There are emerging reports that FM patients can be differentiated from controls by their specific gut-microbiome composition, with either over- or underabundance of some taxa (1). Furthermore, there is report of association between abundance of some taxa and severity of symptoms in FM, including pain intensity, fatigue, sleep disturbance and cognitive symptoms, findings that are independent of dietary differences, comorbidities or disease independent variables. Some of these abundant bacterial taxa are involved in metabolic pathways with effect on FM symptoms that is biologically plausible. It is too early to attribute specific microbes as "bad" or "good" in the context of FM, but further study is needed to explore causal associations between the gut microbiome and FM.

This first step in assessing the microbiome in FM may hold promise for a better understanding of mechanisms operative in FM and other chronic pain conditions, provide hope for a possible biomarker to aid diagnosis and hold potential for therapeutic interventions. At this time, we must still offer patients pragmatic advice regarding good lifestyle practices with attention to a balanced diet, sufficient exercise, and stress reduction, but with the hope that further microbiome study may unlock some of the mysteries of FM and other chronic pain conditions.

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IS-09

AUTOIMMUNE DYSAUTONOMIA

Yehuda Shoenfeld MD, FRCP, MaACR
Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Aviv, Israel.

Chronic fatigue syndrome, fibromyalgia, macrophagic myofasciitis, postural orthostatic tachycardia syndrome, complex regional pain syndrome, post-human papillomavirus vaccine syndrome/human papilloma virus vaccination associated neuroimmunopathic syndrome and sick building syndrome have been noted to share several major clinical features. Three of these disorders are included in the concept of autoimmune/inflammatory syndrome induced by adjuvants (ASIA), which sheds light on their autoimmune pathogenesis. In this paper we summarize the evidence regarding the role of autoimmunity in the seven outlined syndromes with respect to their genetics, autoimmune co-morbidities, immune cell subtype alterations, detection of autoantibodies and presentation in animal models. Furthermore, a symptom cluster of fatigue, dysautonomia, sensory disturbance and cognitive impairment which is common for all the syndromes is identified. We suggest a new concept of autoimmune neurosensory dysautonomia with common denominator of autoantibodies directed against adrenergic and muscarinic acetylcholine receptors with coexistent small fiber neuropathy, which might probably take part in the emergence of these symptoms. Possible modalities of therapy targeting autoimmunity and their efficiency in these seven outlined syndromes are also reviewed. Understanding the suggested concept may assist in identifying the subgroups of patients who may mostly benefit from targeted immunomodulatory therapeutic modalities.

Of therapy targeting autoimmunity in the outlined disorders. ASIA autoimmune syndrome induced by adjuvants, CFS chronic fatigue syndrome, CRP C-reactive protein, CRPS complex regional pain syndrome, FM fibromyalgia, ESR erythrocyte sedimentation rate, HPV human papilloma virus, IVIG intravenous immunoglobulin, MMF macrophagic myofasciitis, ND no data, POTS postural orthostatic syndrome, SCIG subcutaneous immunoglobulin.
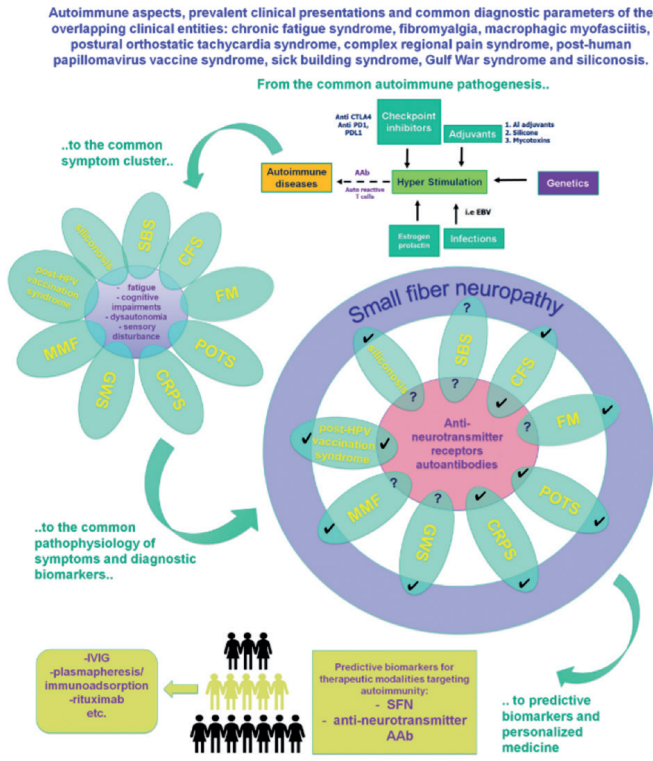
IS-10

"CONSIDER THE TRIGGER" LINKING THE FIBROMYALGIA TO LIFE EVENTS

Dan Buskila
Ben Gurion University in the Negev, Israel.

Fibromyalgia syndrome (FMS) is a polysymptomatic disease, the etiology of which has always been a matter of debate and is still a controversial topic. Anyway, it is now clear the existence of a significant genetic predisposition that creates a familial clustering of the syndrome (1). Starting from this genetic background, FMS symptom development has been linked with various triggers. It was suggested as early as in the 1990s (2) the association between stress and the development of chronic widespread pain and FMS. Stress is the physiological response of the body to a stressor, which is an event or an element able to interfere with the individual's homeostasis. One of the most common examples of a stressor is physical trauma. In fact, a significant physical trauma such as a car accident has been hypothesized to be an important trigger to FMS symptoms (3). Another example could be represented by external organisms and infections that could alter the system's homeostasis (4). Emotional and physical abuse, especially during childhood, are of particular importance and were observed to be significantly associated with the development of FMS (5). In fact, the capability to cope with stressful events is particularly significant for the life of an individual. This is the concept of resilience, and a low coping ability, represented, for example, by catastrophism, was hypothesized to lead to FMS if combined with important life stressors (6). Therefore, the development of resilience-base strategies, by means of, for example, cognitive-behavioural therapy, may be a key factor in treating chronic pain and FMS in particular (7).

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IS-11

HBOT, NEUROFEEDBACK, TMS AND OTHER STORIES: THE NEVER-ENDING LIST OF PHYSICAL THERAPIES FOR FIBROMYALGIA

Roberto Casale MD PhD
Opusmedica, PC&R Patient, Care & Research Network, Piacenza, Italy.

The title of this presentation seems to be tremendously negative toward the so-called physical and complementary therapies for fibromyalgia. Indeed most of the physical therapies so far used showed some benefits to the patient. What we want to stress is not the uselessness of all these treatments that have been used and whose results have published in authoritative journals rather that the substantial similarities of results in average not exceeding 30% of positive response. This puts the accent on some possible factors: 1) a substantial lack of acknowledge of the physiological mechanisms which are at the basis of the use of physical agents to control pain. For instance TENS which is one of the most used electrical therapies is used   without a real acknowledgement of the different neural pathways activated changing intensity duration and frequency of stimulation; 2) some therapies are "unspecific", namely they do not have a defined target as it is for chemical compounds   we are increasingly using more selective and targeted drugs toward one or another mechanism to control pain. For instance some therapies based on mechanical stimulation have more or less the same mechanisms and the studies so far present in literature vary greatly only in the site of stimulation and in the way changes in the nervous system are recorded. In literature, the comparison data between all these techniques are very few and with not perfectly comparable data, do not allow to define which are the best parameters, including the type of stimulus. 3) Another critical point is the empirism used in the application of a physical therapy that is mainly unspecifically application on the painful site. However this way of application do not take into account referred as well as the projected pains.

Another series of criticisms come from the aetiopathogenesis of fibromyalgia. Fibromyalgia must be considered a broad label including forms of fibromyalgia where the physical symptoms are the most relevant and where a targeted physical therapy may be suggested. At the other end of the same rope, the fibromyalgic clinical picture may be dominated by psychological or even psychiatric features. In this last case physical therapies may be just prescribed as possible adjuvants.

Very promising therapies such as the use of hyperbaric oxygen (HBOT) or the use of oxygen in a mixture with ozone (O2O3) have obtained some results by means of an activation a series of broad mechanisms such as the induction of free radicals scavengers and they may be prescribed in a more extensive number of patients. In these cases the critical point is that sometime what is not correct are the parameters measured to ascertain the efficacy of a given therapy.

In this broad range of clinical presentation the prescription of physical therapies should be driven by the clinical picture of the single patient and the decision to prescribe one therapy rather than another must be shared with the patient: heating may be extremely useful in some patients while in other heating may enhance pain, a transcranial stimulation may not be accepted by the patient. Also physical activity has to be chosen in relationship to the actual physical condition of the patient as a normal exercise can be perceived as a physical overload by another patient.

As above stated physical therapies must be used as they are substantially without side effects and may relief symptoms in a non irrelevant percentage

of pain. However more attention must be put on the choice of the therapy and this choice is strongly driven by the clinical picture of the single patient.

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IS-12

ALTERING THE BRAIN THROUGH ALTERNATIVE METHODS

Kati Thieme[1] Delia Hirche[1] Marc G. Mathys[1] Stephen Folgers[2]
[1]*Medical Psychology, Philipps University Marburg, Germany, Germany;*
[2]*Department of Physical Therapy Education, Elon-University, USA.*

Background. Pain and cardiovascular interaction is an important component of the pain regulatory system. This interaction is influenced by baroreflex sensitivity (BRS). Baroreceptor activity through the dorsal medial tractus solitarius (dmNTS) influences somatosensory, cognitive, affective and behavioural components of the pain network.
Objectives. This study tested if 1) Systolic Extinction Training (SET) a combination of baroreceptor training (BRT) and Behavioural Therapy (OBT) would increase BRS, (2) BRS increases central inhibitory changes, and (3) if treatment reduces pain intensity and to what amount.
Methods. Forty-six FM patients and 30 healthy controls (HC) were investigated with a baroreceptor training (BRT) protocol consisting in two 8-minutes-trials where 3 different and randomized electrical stimuli (50%, 75% of individual pain tolerance, and non-painful stimuli) were administered immediately after systolic and diastolic peak of the cardiac cycle. Additionally to BRT, 20 patients were treated with aerobic exercise (AE) and 26 with OBT. Evoked potentials, theta-and alpha-band activity measured with EEG, blood pressure and BRS were measured during treatment sessions before, post, and 12 months after therapy.
Results. The affective (P260) and cognitive (P390) components of pain, but not the attention (N50) and sensory (N150) components, showed significantly greater response in FM vs HCs before therapy (p=0.005). Post SET and in the 12 months follow-up, the EEG components reversed and showed higher theta band activity. SET eliminated pain in 82% (BRS increased 48%) at the 12-month follow-up and BRT+AE reduced pain by 50% in 14% (BRS increased by 11%) of patients.
Conclusion. Alternative methods in FM increase BRS and change sensory, affective, cognitive and behavioural components of pain network resulting in long-lasting pain remission.

IS-13

IMAGING BIOMARKERS OF THE RESPONSE

DM Torta, PhD
Research Group Health Psychology, KU Leuven, Belgium.

The quest for biomarkers in chronic pain syndromes has been in the focus of the research in the pain neurosciences for years. It has generated intense debate about where we stand, whether we have finally identified pain biomarkers, or not (Mouraux and Iannetti 2018, Archibald et al., 2018). Moreover, not all pain researchers enthusiastically joined the search, regarding the patients' experience as the most important criterium for diagnosis and treatment outcome. In the end, a "normalization" of what may be considered an aberrant response does not impact the patients' life, if it is not accompanied by a change in perception. Both the International Association of the Study of Pain (IASP), and a recent relevant consensus paper on the topic (Davis et al., 2017) have underlined that "pain is an unpleasant sensory and emotional experience", and that, as such, the subjective component remains the gold standard. Nevertheless, imaging methods, broadly defined, may complement, especially in certain conditions, the subjective reports. Moreover, they can be used to attempt predictions about the clinical trajectory, in terms of development of chronic pain (*e.g.* post-surgical pain), or suitability

of certain therapeutic approaches over others (*e.g.* cognitive behavioural therapy vs. pharmacological treatment) (Davis et al., 2017). To do so several criteria should be satisfied before an indicator can be considered a reliable biomarker. At present, none of the proposed biomarkers satisfies them all. Indeed, many of the measures await validation in terms of test-retest reliability, specific and/or validity (Davis et al., 2017). To overcome such limitations research is trying to progress in three trajectories. Researchers using fMRI are trying to validate, in healthy volunteers and chronic pain patients (including fibromyalgia patients, López-Solà et al., 2017) Multivariate Pattern Analysis approaches, which would serve as a "signature" for the identification of cortical spatial patterns of pain activation (Reddan and Wager 2018, Wager et al., 2013). This approach constitutes a methodological advance, also in terms of physiological plausibility, to the idea of the "pain matrix". Nevertheless, it is prone to specificity problems, as a signature for pain can be considered as such only if its presence is unique for pain (Iannetti and Hu 2016). What is more, it still lacks normative data that could be used across a wide range of scanners, patients' characteristics, and analysis methods. Gamma Band Oscillations (GBOs) have also been proposed, both in healthy volunteers and in patients, as a biomarker for pain (Zhang et al., 2012, Hu and Iannetti 2019, Gross et al., 2007). The problems with GBOs consist in the absence of test-retest reliability and limited explanatory value. Moreover GBOs are often prone to muscular artefacts (van den Broeke et al., 2017), and above all, not observed when scalp and not intracerebral recordings are used. Due to the positive report bias in research, this latter finding is often underestimated. Finally, a third line attempts to identify markers of central sensitisation, rather than pain per se. Indeed, some authors consider central sensitisation as a potential mechanism, common to several pain syndromes, underlying the transition to chronic pain (Arendt-Nielsen et al., 2018). Recent findings have shown that pupil dilation (van den Broeke et al., 2019) and Reflex Receptive Fields (RRF, Biurrun-Manresa 2014) increase concomitantly with mechanical hypersensitivity (a hallmark of central sensitisation). Of note, while RRF seem to constitute a valid and reliable marker for central sensitisation, it has poor discriminative value between acute and chronic low back pain (Müller et al. 2016).

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IS-14

OVERVIEW OF CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM IN CHRONIC PAIN

David P. Finn

Pharmacology and Therapeutics, Galway Neuroscience Centre and Centre for Pain Research, National University of Ireland Galway, University Road, Galway, Ireland.

Recent years have witnessed intense interest in the potential of cannabis and cannabinoids for effective pain management. Cannabis-based medicines are being approved for pain management in an increasing number of countries worldwide, amidst some uncertainty and controversy on their role and appropriate use. Cannabinoids are the biologically active constituents of the cannabis plant, or their biologically active synthetic analogues, having affinity for, and activity at, cannabinoid (CB) receptors. Two CB receptors have been discovered and characterized: CB_1 and CB_2. Furthermore, endogenous cannabinoids (endocannabinoids) are synthesized in most tissues and organs of humans and other animals and act at CB receptors to regulate numerous physiological and pathophysiological processes, including pain. For example, endocannabinoids are a key component of the endogenous analgesic system, and mediate stress-induced analgesia. Moreover, elevation of endocannabinoids within the somatosensory system or in discrete brain regions implicated in pain, modulates nociception. There are now thousands of published studies demonstrating antinociceptive effects of phytocannabinoids (*e.g.* delta-9-tetrahydrocannabinol [THC]), synthetic CB_1 or CB_2 receptor agonists, and drugs that elevate endocannabinoid levels in animal models of acute and chronic pain. Sites of action include peripheral primary afferent neurons, the dorsal horn of the spinal cord and discrete brain regions implicated in pain processing. Mechanisms of action include attenuation of nociceptive transmission, activation of descending pain modulatory pathways, anti-inflammatory effects, and neuroimmune modulation. The complexity and multitude of targets within the endocannabinoid system presents an opportunity for rational design of novel analgesics with favourable side-effect profiles. Relative to preclinical studies, there are far fewer clinical trials of cannabinoids or cannabis for chronic pain. There is some limited evidence from clinical trials for efficacy in specific types of chronic pain (*e.g.* neuropathic pain, cancer pain), but further studies with larger sample sizes, of longer duration, with a broader range of drugs, formulations and routes of administration, and in other types of pain, would be very welcome. Challenges to clinical trials with, and regulation of, cannabinoids/cannabis include their legal/illegal status in many countries, potential psychoactivity and implications for blinding studies, complexity of plant-based medicines, funding for large-scale trials, and attitudes and education of both doctors and patients. A recent European Pain Federation (EFIC) Position Paper on the topic recommended that therapy with cannabis-based medicines should only be considered by experienced clinicians as part of a multidisciplinary treatment and preferably as adjunctive medication in properly selected and supervised patients if first and second line therapies have not provided sufficient efficacy or tolerability (Häuser *et al.*, 2018; Starowicz and Finn, 2017; Woodhams *et al.*, 2017). This Position Paper advised that the quantity and quality of evidence are such that cannabis-based medicines may be reasonably considered for chronic neuropathic pain and that for all other chronic pain conditions (cancer, non-neuropathic non-cancer pain), the use of cannabis-based medicines should be regarded as an individual therapeutic trial. In summary, the endocannabinoid system plays a key role in regulating pain, and a large body of preclinical research supports the contention that cannabinoids and/or modulators of the endocannabinoid system are promising novel analgesic agents. Further clinical research and trials are warranted, alongside continued preclinical elucidation of targets, mechanisms and candidate drugs.

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IS-15

OPIOIDS (INCLUDING OPIOID ANTAGONISTS) AND CANNABINOIDS FOR FIBROMYALGIA AND CHRONIC PAIN - IS THERE ANY ROLE?

Laura Bazzichi[1], Arianna Consensi[1], Camillo Giacomelli[1], Piercarlo Sarzi Puttini[2]
[1]*U.O. of Rheumatology, Pisa A.O.U.P, Pisa, Italy;*
[2]*U.O. of Rheumatology, L. Sacco University Hospital, Milan, Italy.*

Fibromyalgia is a syndrome characterized by widespread pain, fatigue, sleep disturbances and a constellation of dysfunctional symptoms, which lead to poor quality of life and negative consequences for patients' family and work life. People affected by fibromyalgia have no specific changes in blood and instrumental tests and there is no specific therapy for the disease. Patients easily develop adverse effects to drug therapies, hardly withstand physical therapies and even psychological therapies are not always readily available and specific.

Fibromyalgia syndrome appears to be a chronic disturbance characterized by central sensitization, whose typical clinical manifestations are hyperalgesia and allodynia, also associated with chronic peripheral stimuli. Among the various etiopathogenetic hypotheses formulated for fibromyalgia, alterations of the endocannabinoid and opioid systems probably play an important role. Both of these systems are activated primarily in conditions of cellular stress and in response to pain; they are interactive and changes in one of the two systems induce negative or positive feedback mechanisms in the other. Indeed, there is growing evidence on the positive effects of Cannabis Sativa for fibromyalgia, with effects on chronic pain, sleep, rigidity, gastrointestinal disorders and general well-being depending on different concentrations of its active ingredients (tetrahydrocannabinol and cannabidiol) and on the way of administration. On the contrary, treatment with strong opioids in fibromyalgia has proven to be a failure in the majority of cases, because of not only ineffectiveness, but also many adverse events, as for example the hyperalgic syndrome. Therefore, the use of opioids antagonists such as naltrexone may be promising. If used at low doses (1 to 5 mg), naltrexone has a neuroprotective effect, since it acts as a glial modulator, inhibiting microglial activation. Furthermore, it elicits the so-called rebound effect of the opioids, since a transitory block of the opioid receptor increases opioid endogenous production.

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IS-16

MAKING PEACE BETWEEN DOCTORS AND CANNABINOIDS (AND LESSONS LEARNED FROM COUNTRIES AROUND THE WORLD)

Howard Amital MD MHA
Department of Medicine 'B', Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel.

During the last century, the history of cannabis has been rewritten several times; the once commonly used natural remedy had been criminalized, faded into oblivion, resurrected and undergone a recent interesting process of medicalization.

In several countries, Health ministries legislated paths for legal permits for the use of cannabis to many patients, primarily to patients suffering from continuous and troublesome pain.

Recent retrospective analyses had marked an impressive effect of cannabis extracts used either by smoking, inhalation or sublingually on many func-

tional, mental and pain parameters. These interesting results are even more challenging given the borderline outcomes of the current medical agents that had been approved by the FDA and EMEA. Of course the need for properly designed prospective studies are in need; it seems that such studies are pending and will contribute to the harnessing of cannabis for medical use.

IS-17

FOCUSING ON EARLY DIAGNOSIS, REHABILITATION AND PREVENTION

Marco Di Carlo, MD
Rheumatological Clinic, Università Politecnica delle Marche, Ospedale Carlo Urbani, Jesi (Ancona), Italy.

Fibromyalgia (FM) is a complex chronic pain condition that affects at least 2% of the adult population in Western countries. The diagnostic difficulties are still many for this disease, and justify a diagnostic delay of more than two years on average.

Over the years, multiple sets of diagnostic/classification criteria have been developed. While the criteria of the American College of Rheumatology of 1990 have been widely used for two decades, their application has been overcome by the adoption of the 2010 ACR criteria, which introduced for the first time the concepts of widespread pain index (WPI - a scale from 0 to 19) and symptom severity (SS - a scale from 0 to 12), whose sum defines the polysymptomatic distress scale (PDS - a scale from 0 to 31). While the 1990 ACR criteria were mainly criticized for the difficulty, especially by non-rheumatologists, to correctly perform the tender point count, the 2010 ACR go beyond the need to perform an objective examination. They were subsequently continued in 2011 and 2016, and the various sets of ACR criteria confirmed their robustness. In particular, in the 2016 ACR criteria widespread pain is defined as pain in at least four of the five regions (excluding jaw, chest and abdominal pain), specifying the symptoms covered in the SS as headache, pain or cramping in the lower abdomen, and depression. These criteria specifically state that "a diagnosis of FM is valid independently of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important diseases". More recently, Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) (AAPT) introduced new criteria for FM focused on (1) multi-site pain (MSP), defined as 6 or more pain sites from a total of 9 possible sites, (2) moderate to severe or fatigue sleep problems, (3) MSP plus fatigue or sleep problems must have been present for at least 3 months. Sensitivity, specificity and diagnostic performance, especially in early stages of disease, of each set of criteria should be evaluated in future studies.

Linked to the concept of early diagnosis are the currently available screening tools, which help the early identification of key symptoms of FM, and the concept of prevention. Factors that can predict the onset of FM are still largely unknown, although some genetic characteristics, some adverse life experiences, poor response to stress and some trigger events are recognized as predisposing factors to the onset of FM.

From the rehabilitation treatment point of view, it has a pivotal role in FM management. The 2017 EUropean League Against Rheumatism guidelines established its importance (strong for recomedation, 100% agreement), particularly in terms of physical exercise (both aerobic and strengthening exercise). Thanks to the current possibilities provided by Information and Communication Technologies, exercise can be dispensed at home and conducted safely by patients independently.

IS-18

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN PRIMARY FIBROMYALGIA AND CHRONIC FATIGUE SYNDROME

Enrico Brunetta[1], Dana Shiffer[1], Franca Barbic[1], Franca Dipaola[1], Pietro Mandelli[2], Sara Achenza[3], Marco Folci[1], Aurora Zumbo[1], Maura Minonzio[1], Beatrice Cairo[4], Laura Boccassini[5], Piercarlo Sarzi-Puttini[5], Alberto Porta[4,6], Raffaello Furlan[1,7]
[1]Internal Medicine, [3]Nephrology, Humanitas Clinical and Research Center-IRCCS, [7]Humanitas University, Rozzano, Italy; [2]Dept. of Pathophysiology and Transplantation, University of Milan, Italy; [4]Dept. of Biomedical Sciences for Health, University of Milan, Italy; [5]Reumathology, L. Sacco Hospital, ASST Fatebenefratelli Sacco, Milan, Italy; [6]Dept. of Cardiothoracic, Anesthesia and Intensive Care, IRCCS-Policlinico San Donato Milanese, Italy.

Primary Fibromyalgia (F) and Chronic Fatigue Syndrome (CFS) are both chronic disabling diseases characterized by elusive etiopathologies. During the upright position, F and CFS share common symptoms, including pain, fatigue, palpitations, dizziness and orthostatic intolerance. This highlights a relevant comorbidity with other dysfunctions of cardiovascular orthostatic homeostasis such as the reflex syncope and Postural Tachycardia Syndrome (POTS). Symptoms and physical signs point to abnormalities in the cardiovascular autonomic control that will be briefly discussed.

In F, data from our laboratory obtained by spectrum analysis of heart rate and blood pressure variability and by sympathetic microneurography recordings, suggested the presence of an overall increased sympathetic activity and decreased cardiac vagal modulation while supine, compared with controls (1). Notably, the enhanced sympathetic activity might play a role as a promoter of chronic pain (2).

In the up-right position, F patients showed bunted capability to increase the sympathetic activity to the vessels and decreased cardiac vagal modulation compared with controls. These findings may account for the exceedingly high frequency of syncope during orthostatic challenge in such a population (1).

A recent meta-analysis on the autonomic changes attending CFS concluded for a greater heart rate and LF/HF index in CFS than in controls while supine (3). These findings suggest the presence of cardiac sympathetic overactivity in CFS, similarly to what we observed in F (1). Orthostatic heart rate was greater in CFS than in controls (3), mimicking the haemodynamic pattern characterizing POTS (4). In addition, heart rate variability parameters during orthostasis were similar in CFS and controls (3), in spite of the high rate of orthostatic dizziness (45%) and fainting (43%) characterizing CFS (3). Thus, additional non-autonomic mechanisms may affect orthostatic tolerance in CFS. Among those, reduced left ventricular chamber, with low cardiac output due to gravitational and exercise deconditioning, might contribute to orthostatic intolerance (3, 5).

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IS-19

CAN THE WAY WE THINK CHANGE THE WAY WE PERCEIVE PAIN?

Riccardo Torta
Full Professor of Clinical Psychology, Department of Neuroscience, University of Turin, Italy.

According to the bio-psycho-social model, pain perception is not only linked to somatic components, but is strongly influenced by emotional, cognitive and social aspects. Mood depression, similarly to anxiety and chronic stress, favours pain through a central sensitization and a reduction of the pain sub-threshold, as confirmed by epigenetic and clinical studies (Satyanarayanan *et al.*, 2019; Shigetoh *et al.*, 2019). On the other hand, the relationship between mood and pain is not only of co-morbidity, but it is also of co-pathogenesis, because the two pathologies share similar background aspects, such as neurotrasmettitorial, immune and hormonal ones. In its turn also cognition can influence pain perception through several mechanisms, such as attention, expectation, fear, memory, etc. that are mostly interconnected. Directing attention towards a painful stimulus seems to increase its perceived intensity. On the other hand, distraction reduces pain perception, as well clinically evidenced by psychological interventions, such as hypnosis, mindfulness, imagery, etc. that nevertheless work on different cognitive aspects. For example fMRI studies from hypnosis show a decreased activity in the thalamus and long term mindfullnes induces a deactivation of prefrontal cortex (Casiglia *et al.*, 2020; Vanhaudenhuyse *et al.*, 2014). Nevertheless neuroimaging techniques can show important confounding factors and it is under discussion if neuroimaging techniques are suitable to measure attention, and, particularly, the attentional modulation of pain (Torta DM *et al.*, 2017). Another approach is the evaluation of the event-related brain potentials (ERPs), elicited by nociceptive stimuli. They are largely influenced by vigilance, emotion, alertness, and attention and can represent neurophysiological indexes of the processes underlying detection and orientation of attention toward the eliciting stimulus (Legrain *et al.*, 2012).

Pain-related fear has been implicated in the transition from acute to chronic pain and its persistence: fear of pain can further stimulate avoidance behaviors that contribute to the avoidance of many activities, leading to inactivity and, ultimately, to greater disability. Pain-related fear has been implicated in the transition from acute to chronic pain and its persistence and it is particularly evident in catastrophising Patients (Khalid and Tubbs, 2017).

Expectation, is usually associated with learning (mainly concerning past experiences), and can be one of the most relevant background of the placebo effect.

The placebo effect (expectation for pain relief) releases endogenous opioids and facilitates analgesia, strengthening exogenously administered opioids. Nocebo hyperalgesia (expectation for persistent or worsening pain) opposes endogenous opioid analgesia. The placebo component can act on any kind of therapeutic intervention, making more efficacious an antalgic treatment, through a releases of endogenous opioids and facilitates analgesia from exogenously administered opioids. In his turn, the nocebo hyperalgesia (expectation for persistent or worsening pain) opposes endogenous opioid analgesia and reduces the effectiveness of a cure, counteracting, almost in part, the biological antalgic activity of a treatment. In this way, contextual factors (CFs) are clinically relevant: the presence of positive CFs, can reduce pain by producing placebo effects, while a negative context, characterized by the presence of negative CFs, can aggravate pain by creating nocebo effects.

A strictly related aspect is suggestion: instruction (*e.g.* thorugh psychoeducation) and suggestions (for example by hypnosis) can have a powerfull effect on pain and emotions. This activity is mediated by modifications in prefrontal systems, responsible for the top-down control and the generation of affective meaning

Memory and learning processes play an important role in persistent pain: actually the hippocampal formation and neurogenesis are involved in the development and maintenance of persistence of pain (McCarberg and Peppin, 2019).The mechanisms that underlie pain plasticity, following injury, show a striking resemblance to molecular mechanisms involved in learning and memory processes in other brain regions, including the hippocampus and cerebral cortex (Price and Inyang, 2015). In several Patients with pain the inability to extinguish painful memory trace leads to a pain chronification. Central synapses, especially excitatory synapses, are undergoing long-term memory-like plastic changes after peripheral injury Long-term potentiation (LTP), a key cellular model for learning and memory, is reported in the anterior cingulate cortex (ACC) and insular cortex (IC), two key cortical areas for pain perception emotional changes.

In this way, chronic pain has to be prevented as early as possible, in order to keep ''pain memory'' from being established (Prakash and Golwala, 2011).

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IS-20

DO GENDER, RACE AND RELIGION PLAY A ROLE IN FIBROMYALGIA?

Jacob Ablin
Tel-Aviv Sourasky Medical Center, Israel.

While in the past the so-called "Yuppie syndrome", more or less overlapping with what we now classify as the chronic fatigue syndrome, was implicitly considered to be associated with a particular socio-economic class, subsequently it has been demonstrated that at least when considering the closely related syndrome of fibromyalgia (FMS) – it is definitely not restricted to any particular class or culture. In fact, epidemiological studies have documented FMS to be prevalent basically wherever researchers have searched for it – over vastly different geographic and cultural settings. Nonetheless, this does not imply that ethnic factors do not play any role in chronic pain in general as well as in FMS in particular.

A considerable amount of existing research points towards the fact that racial and ethnic minorities suffer more serious outcomes as a result of chronic pain, as well as suffering from higher disability and limitation of work activity. Part of this phenomenon may be the unfortunate result of minorities receiving a lower quality of pain care in countries such as the USA (1). This outcome may result from factors such as lack of insurance, delayed access to care as well as difficulties in communication with healthcare providers. Racial differences have however also been identified both in clinical as well as experimental pain, particularly when comparing African Americans with non-Hispanic whites. In a range of chronic pain conditions, including osteoarthritis and migraine, more severe levels of pain have been documented among individuals belonging to ethnic and racial minorities. Moreover, when studying specific mechanisms involved in centralized pain conditions such as Diffuse Inhibitory Noxious Control (DNIC), (currently usually termed conditioned pain modulation or CPM), significantly greater inhibition of pain was documented among non-Hispanic white participants when compared with African Americans (2), indicating an inherent racial difference in pain modulation. When analyzing chronic pain according to the biopsychosocial paradigm, three separate components are evaluated, including the sensory-discriminative, the cognitive-evaluative and the affective-motivational (3). While sensory-discriminative features of pain (*e.g.* pain thresholds) appear to be relatively constant among racial and ethnic groups, affective and motivational aspects appear to be more closely linked with ethnicity.

The possible role played by religion and spirituality in the modulation of chronic pain is another intriguing field of research. Religiosity and spirituality are often considered to provide resilience and support to individuals suffering from chronic disease, but their role in chronic pain is less clear. Moreover, sell – efficacy and cognitive constructs such as internal locus of

control are often considered to be beneficial in the management of chronic pain, and are considered targets for cognitive behavioral treatment (CBT), but their interaction with religious belief in not obvious. Some preliminary results have indicated that in FMS patients, higher levels of religiosity/spirituality appears to be inversely correlated with specific outcome measures. While it is possible that more severe symptoms may lead patients towards higher levels of religiosity (and not vice versa) this association calls for further elucidation. In addition, the possible role of different world religions and sets of belief in the modulation of chronic pain is an area of interesting investigation.

Last but not least, the role of gender in chronic pain is both well-known as well as incompletely understood. Chronic pain conditions such as FMS are known to be much more prevalent among females compared with males, although with changing sets of criteria it has become clear that this predominance is not as overwhelming as previously thought. The etiology of these differences is not well understood although it is tempting to consider hormonal influences. In one intriguing preliminary study, FMS was found to be more prevalent among transgender men than among transgender women, indicating that early life, or *in utero* effects may play an important role in determining an individual's tendency to developed chronic centralized pain. Thus, physicians treating patients suffering from chronic pain and FMS, should be aware of the complex roles of race, ethnicity, religion and gender on their patients; further interdisciplinary research is called for in this field.

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IS-21

FIBROMYALGIA PERSONALITY: WHAT IS IT?

Bárbara Gonzalez, Rosa Novo & Telmo Baptista
University Lusophone of Humanities and Technologies, Portugal.

We intend to discuss Fibromyalgia (FM) personality based on empirical findings of a structured sequence of studies. This discussion is epistemologically anchored in the Relational Paradigm, which describes a dynamic system of self-organization of meanings through which the individual transforms the world in which he lives in, and transforms himself through experience (Overton, 2013). Theoretically, this discussion is linked with the concept of personality of McAdams (1996; 2010) which comprises the following three interdependent levels, with a reciprocal influence on each other: the dispositional traits (level 1); motivational, social-cognitive, and developmental adaptions, contextualized in time, place and/or social role (level 2); the integrative life stories or personal narratives, that people construct to make meaning and identity (level 3). The different kinds of empirical data, both quantitative and qualitative, are discussed in their relation to the different levels, to achieve a global comprehension of personality of FM female patients.

Regarding some of the main empirical findings, a meta-analysis has showed significantly higher values of a broad range of negative personality and psychopathology features in the FM group, comparing with healthy controls. After this starting point, a study compared FM with rheumatoid arthritis (RA) patients, and FM patients was characterized by clinically significant values of extreme somatic complaints, the neurotic triad, feelings of unworthiness and inadequacy, great psychological turmoil, and unusual beliefs and great sense of lack of adequacy, while the RA patients had no pathological features. Secondarily, FM patients were characterized by significantly higher feelings of ineffectiveness, pessimism, intense emotional distress, defensiveness and emotional overcontrol, lack of achievement orientation, sensitivity to criticism and inability to tolerate stress, lack of self-esteem and self-confidence. Finally, the heterogeneity regarding personality and psychopathology profiles, suggested in the mentioned meta-analysis, was partially confirmed, as within a sample of FM patients only, one group had no clinically significant personality psychopathology features, while the other group had clinically significant levels of negative emotionality and introversion, a combination of personality psychopathology in line with Type D personality. It is relevant that the mean levels of introversion are even

higher than the neuroticism ones, preventing this group from the protective role the presence of positive affect may have against the experience of negative affect, when facing stress and pain.

Beyond heterogeneity, some aspects seemed to be common to all FM patients, showing the relevance of psychological intervention as part of any medical intervention: significantly high values of neurotic aspects, but also reflecting social alienation, unusual beliefs and confusion, which differentiates FM from other chronic pain samples, in which the neurotic aspects only are normally salient. Low ego strength and high health concerns, which go beyond physical concerns, and better reflects the psychological representation of health problems, are also common core features.

In sum, the empirical data suggest that there may be specific psychological characteristics associated to FM (*i.e.*, differentiated from healthy individuals and RA), namely personality, having the level of psychological processes and motivations (level 2) as the common core. Some of the FM patients have severe features, compatible with level 1 personality disorders (*i.e.*, structural characteristics, relatively stable and enduring). In this case, the pathological features affect the adaptive styles, goals in life, motivations, self-image and the identity core (level 3).

IS-22

CASE VIGNETTES: DEALING WITH FIBROMYALGIA WHEN YOU HAVE 10 MINUTES PER PATIENT…

Valeria Giorgi
Rheumatology Unit, ASST-Fatebenefratelli L. Sacco University Hospital, Milan, Italy.

Dealing with fibromyalgia in daily clinical practice implies the existence with two different points of view: the one of the patient and the one of the doctor. The problem is to make these two positions meet on a common ground, since they are very much apart.

Fibromyalgia patients usually come from years of consultation with various specialists (1, 2). They have been told any type of things, from the fact that their disease is present "just in their head", to the most imaginative diagnoses. Therefore, they sit in the waiting room confused, in need of detailed explanations, and full of questions to be asked to the doctor they are about to see. For example, they want to know whether they have a "real" disease, or, if they are already aware of their diagnosis, whether their disease is progressively invalidating and which would be the prognosis.

On the other hand, there is the situation in the doctor's perspective. Especially in this moment, hospitals have not the possibility to hire enough physicians so that patients' requests are fulfilled: hence, doctors are exhausted by night shifts and by uncountable hours spent in their outpatient clinic. They deal with dozens of patients during the same morning and they are constantly beyond schedule.

With this picture in mind, it is clear that there will be the creation of a contrast: between fibromyalgia patient, who has particularly more needs of being listened to and of receiving explanations, and the doctor, who is allowed to talk with his or her patients for just ten minutes. The consequence of this contrast will be dissatisfaction, on both sides: the doctor will be disappointed by the inability of the health system to deal with chronic patients, while fibromyalgia patient will feel frustration because of the lack of sufficient explanations and care.

It is clear that finding a definitive solution of this problem is beyond the capability of this relation. Anyway, we can subdivide the problem in two parts. On the one hand, there is the need of a better education of physicians on fibromyalgia (3), bearing in mind also the biopsychosocial model of medicine, with the aim of avoiding paternalistic ways of treating patients via a trivialization of their feelings; on the other hand, there is the strong necessity of reforming and improving the national health system part that deals with chronic patients, and in particular fibromyalgia patients, who need a clear recognition of their disease and the establishment of a unique diagnostic and therapeutic pathway, shared by the GP and by various specialists.

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IS-23

SCREENING FOR FIBROMYALGIA IN GENERAL PRACTICE

Alberto Batticciotto, MD, PhD
Rheumatology Unit - Internal Medicine Department, Ospedale di Circolo, Fondazione Macchi, ASST, Settelaghi. Varese, Italy.

Fibromyalgia (FM), defined as a chronic widespread pain syndrome accompanied by fatigue, sleep disturbance, cognitive dysfunction and several other associated symptoms (*e.g.* headache, pain/cramps in the abdomen, numbness/tingling, dizziness, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms) or coexisting painful conditions (*e.g.* psychological distress, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, chronic pelvic pain, temporomandibular pain disorder, restless leg syndrome, and systemic exertion intolerance disease) is a quite common disease with a reported prevalence ranging from 2 to 6% in case of patients attending general practitioners, 5 to 8% in hospitalized patients and 14 to 20% in rheumatology consultations. (1-3)
Studies in primary care settings confirmed that up to 1 in 20 patients has FM symptoms with a growing trend due to an increasing knowledge of the disease. However, the wild range of symptoms and the gradual evolution of FM, make it difficult to diagnose the disease in primary care settings and often require different specialist referrals and several instrumental tests. For this reason, studies reported a worldwide median delay in diagnosis ranging from 2.6 to 5 years (4) and a median numbers of referrals of 3.7 physicians before receiving a diagnosis. (5) The continuous passage from specialist to specialist leads patients to receive multiple drugs to treat the single different symptoms, delaying the correct multimodal and multidisciplinary approach, and to undergo multiple instrumental tests amplifying healthcare costs.
With the 2016 revision of the 2010/2011 ACR criteria, authors combined the 2010 "physician" based criteria with the 2011 modified "patient" criteria into a unique set of criteria with the aim to obtained useful tool for daily clinical practice diagnosis. Furthermore, the 2017 "EULAR revised recommendations for the management of fibromyalgia" summarized the last decade of scientific evidence in order to help physician in the pharmacological and non-pharmacological management of fibromyalgia patients. (6, 7)
The knowledge and the correct use of the international criteria and current management guidelines would allow to create a patient-centric multidisciplinary approach in primary care setting for the majority of FM patients able to improve outcomes and to optimize use of healthcare resources.

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IS-24

THE IMPORTANCE OF MENTAL HEALTH CARE SPECIALISTS

Winfried Häuser
Klinikum Saarbrücken, Germany.

Psychosocial variables are of major importance in the predisposition, triggering and development of the chronicity of fibromyalgia symptoms in most (not all) patients. Childhood adversities such physical and sexual abuse, life events and trauma might predispose a person to the development of FMS. Psychosocial stress (*e.g.* workplace and family conflicts might trigger the onset of chronic widespread pain and fatigue. Depression and post-traumatic stress disorder increase somatic and psychological symptom burden and increase disability. I will point out how some of these psychological factors might be associated with central sensitization.
Current guidelines (*e.g.* European League Against Rheumatism) recommend a stepwise approach in the management of FMS. Mental health care specialists should be included in the care of patients with severe forms of FMS. There are systematic reviews available which demonstrate the efficacy of some psychological therapies, *e.g.* traditional cognitive behavioral therapies, hypnosis, in reducing psychological distress and disability – if compared to waiting list controls or treatment as usual. However, psychological therapies are not superior to other active therapies, *e.g.* aerobic exercise or individualised treatment with duloxetine and /or pregabalin. In contrast to drug therapies, sustained positive effects of psychological therapies can be found at long-term follow-up.
High quality single studies with acceptance-based psychological (*e.g.* Acceptance and Commitment Therapy) and psychodynamic (*e.g.* Emotional Awareness and Expression Therapy) approaches have enriched the portfolio of mental health care specialists. Based on my clinical experience, I will point out which psychological therapy might be appropriate for which psychological situation in FMS.
There are two major obstacles to an optimal management of FMS-patients by mental health care specialists: Misbeliefs about the nature of FMS and limited availability and /or access in most countries of the world. I will point out some of the myths of psychiatry and psychosomatic medicine pertaining FMS and which innovative approaches (*e.g.* internet-based psychological therapies) might increase access of patients to methods to reduce psychological distress and disability and to increase life satisfaction.

IS-25

WHO SHOULD BE TREATING FIBROMYALGIA PATIENTS?

Piercarlo Sarzi-Puttini, Valeria Giorgi
Rheumatology Unit, ASST-Fatebenefratelli L. Sacco University Hospital, Milan, Italy.

Fibromyalgia is a chronic widespread pain disease also characterized by other subjective symptoms such as fatigue, sleep disturbances, autonomic abnormalities and neurocognitive difficulties. Moreover, patients are usually affected by regional pain syndromes, such as irritable bowel syndrome or migraine, and mood disorders, such as anxiety and depression. It has been hypothesized that fibromyalgia pain may arise from central nervous system morphological changes 1 and/or from peripheral neuropathy 2. So, fibromyalgia appears as a complex, polysymptomatic syndrome that cannot be pigeon-holed in a predetermined specialty, but it encompasses many of them - mainly algology, neurology, rheumatology, psychiatry and rehabilitation medicine. Hence, the question of who should manage and follow-up these patients arises, in particular because it is a chronic pain syndrome whose symptoms are very variable in a long-term perspective and can be severely invalidating. Therefore, a multidisciplinary approach is necessary, in which specialized and nonspecialized physicians interact in a strict manner with other healthcare professionals.
In the first steps of disease diagnosis, the specialist may be indispensable. In fact, diagnosis could be quite difficult to make, because usually all the symptoms are not present at the same time in the same patient but follow an undulating behaviour along the disease course. Thus, although screening tests that are feasible to be used in the general practitioner's daily practice exist, diagnosis is generally designated to a more experienced specialist (usually the rheumatologist), to whom more complex cases are particularly

important to be referred, especially if there are concomitant laboratory test abnormalities. After a proper diagnosis is done, an appropriate therapeutic strategy should be set up. Since fibromyalgia is a polysymptomatic disease with a multifactorial aetiology, its therapy should be multimodal, and essentially based on three pillars: 1) patient education and fitness; 2) pharmacological therapy; 3) psychotherapy. Patient education and initiation of a structured exercise plan are the most important pillars of fibromyalgia treatment and could be given to each patient by the general practitioner. He or she may also be important to prevent the development of fibromyalgia pain in a predisposed population, namely the one suffering from regional pain syndromes or chronic peripheral pain diseases, which can sensitize the nervous system in a bottom-up fashion (3). On the other hand, the initiation of a specific pharmacological therapy could be more difficult for a nonexperienced physician. The therapy of more severe cases, which were estimated to be one-third of total fibromyalgia population (4), could be set by the specialist, who is usually a rheumatologist or an algologist. The follow-up of the patient can afterwards be carried out by an integrated network including not only specialized and nonspecialized physicians, but also other healthcare workers, such as the rehabilitation and occupational therapist, the psychologist and the physiotherapist (5).

Last but not least, the creation of such an organized network, comprising a systematic and codified diagnostic-therapeutic pathway, would be essential to avoid that depressed and frustrated patients, whose disease is not recognized or treated in an appropriate, multidisciplinary manner, put themselves in the hands of charlatans who promise the ultimate cure for fibromyalgia.

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O-01

BLUNTED CARDIOVASCULAR RESPONSES TO ORTHOSTATIC AND CLINOSTATIC POSTURE CHANGES IN FIBROMYALGIA: FURTHER EVIDENCE OF A UTONOMIC ABNORMALITIES IN THE DISORDER

Ana M. Contreras-Merino[1], Dmitry M. Davydov[2], Gustavo A. Reyes del Paso[1]
[1]*Department of Psychology, Faculty of Humanities and Education Sciences, University of Jaen, Spain;* [2]*Laboratory of Neuroimmunopathology, Institute of General Pathology and Pathophysiology, Russian Academy of Sciences, Russia.*

Background. Fibromyalgia is associated with autonomic nervous system abnormalities. At the cardiovascular level, some studies have found reduced heart rate reactivity to psychological and physical stressors, including tilt maneuvers.
Objectives. To evaluate the temporal dynamics of short-term beat-to-beat cardiovascular responses to orthostatic and clinostatic postural changes in fibromyalgia patients.
Methods. Heart rate, systolic and diastolic blood pressure, and total peripheral resistance were derived using electrocardiography, impedance cardiography, and continuous beat-to-beat blood pressure recordings in 47 fibromyalgia patients and 37 healthy controls. The procedure included: (1) a 5-minute baseline in a sitting position; (2) 1 minute standing (first orthostatic phase); (3) 5 minutes lying down (clinostatic phase); (4) 5 minutes standing (second orthostatic phase). Differential second-by-second scores (with respect to baseline means) were obtained from the 30 first seconds of each phase.
Results. Interactions Group x Seconds indicated reduced increases in heart rate and cardiac output during the standing phases and reduced decreases in heart rate during the lying phases in fibromyalgia patients in comparison with healthy participants. Averaged diastolic arterial pressure was greater during standing, and systolic arterial pressure and peripheral total resistance were greater during lying in fibromyalgia than controls, while mean arterial pressure was greater both during standing and lying in fibromyalgia in comparison with healthy individuals.
Conclusions. Further evidence of blunted autonomic responses to physical stressors was observed, supporting the existence of autonomic dysregulations in fibromyalgia. The inclusion of continuous measures may provide information about the time dynamics and delayed adaptation periods in this disorder.

O-02

THE RELEVANCE OF VARIANTS OF CONNECTIVE TISSUE (HYPERMOBILITY) TO FIBROMYALGIA, ME/CFS AND CONTROVERSIES SURROUNDING DIAGNOSTIC CLASSIFICATION

Jessica Eccles[1,2,3,4], B Thompson[1], K Themelis[1], M Amato[1], R Stocks[1], A Pound[1,4], A-M Jones[4], Z C Cipinova[2], L Shah-Goodwin[2], J Timeyin[2], C R Thompson[2,5,6], T Batty[1,2,7], NA Harrison[1,8], HD Critchley[1,9,10], K A Davies[2,5,6].
[1]*Neuroscience, Brighton and Sussex Medical School, UK;* [2]*Clinical Investigation & Research Unit (CIRU), Brighton and Sussex University Hospitals NHS Trust, UK;* [3]*Immunopsychiatry Service, Sussex Partnership Foundation NHS Trust, UK;* [4]*Research and Development, Sussex Partnership Foundation NHS Trust, UK;* [5]*Dept. of Clinical and Experimental Medicine, Brighton and Sussex Med School, UK;* [6]*Dept. of Rheumatology, Brighton and Sussex University Hospitals NHS Trust, UK;* [7]*Dept. of Medical Education, Brighton and Sussex Medical School, UK;* [8]*Immunopsychiatry Research Group, Cardiff University Brain Research Imaging Centre, UK;* [9]*Sackler Centre for Consciousness Science, University of Sussex, UK;* [10]*Sussex Partnership NHS Foundation Trust, UK.*

Background. Fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have overlapping symptoms. Complexity may have contributed to consideration of both as functional disorders. Shared symptoms have fueled debate as to whether they are manifestations of the same spectrum or separate entities. Both are associated with hypermobility.
Objectives. To understand the relevance of hypermobility to symptoms in Fibromyalgia and ME/CFS
Methods. We report part of a larger case-control study exploring mechanisms of chronic pain and fatigue (ISRCTN78820481). Participants were

assessed for symptomatic hypermobility (Brighton Criteria and hEDS Criteria): 63 presented with a confirmed diagnosis of either Fibromyalgia and or ME/CFS; 24 participants were healthy controls.

Results. 32% of patients had received a diagnosis of Fibromyalgia; 38% ME/CFS and 30% dual diagnoses. After research evaluation, 89% met ACR diagnostic criteria for fibromyalgia; 94% Canadian Criteria for ME/CFS; 97% Fukada Criteria for ME/CFS. 85% in met diagnostic criteria for Fibromyalgia and ME/CFS on all three sets of tools (ACR, Canadian, Fukada). In addition, 81% of patients met Brighton Criteria for joint hypermobility syndrome and 18% the 2017 hEDS criteria, significantly greater than controls. Of participants with the disorder only one in four had received a prior diagnosis of hypermobility.

Membership of the patient group was predicted by meeting the Brighton Criteria (p=0.001, OR 7.08), but not by meeting the hEDS criteria. The historical, rather than current Beighton score correlated with; 1) total pain (p=0.03); 2) widespread pain (p=0.01); 3) symptom severity (p=0.01) and 4) fatigue impact (p=0.028).

Conclusions. Symptomatic hypermobility is relevant to Fibromyalgia and ME/CFS, poorly understood conditions that have a considerable impact on quality of life. It is important to note the high rates of mis/underdiagnosis of symptomatic hypermobility in this group and the relative predictive value of criteria. Our observations have implications for diagnosis and treatment targets.

O-03

TEMPERATURE RELATED TO PERIPHERAL VASCULAR FLOW OF THE HANDS AND THE PRESSURE PAIN HYPERSENSITIVITY IN FIBROMYALGIA PATIENTS

Jamal El Mansouri Yachou[1], María Correa Rodríguez[2],
Antonio Casas Barragán[1], Rosa María Tapia Haro[1],
Francisco Molina Ortega[3], María Encarnación Aguilar Ferrándiz[4]
[1]*Dept. of Physical Therapy, Faculty of Health Sciences, University of Granada, Spain;*
[2]*Department of Nursing, Instituto de Investigación Biosanitaria de Granada, Faculty of Health Sciences, University of Granada, Spain;*
[3]*Department of Health Science, University of Jaén, Spain;*
[4]*Department of Physical Therapy, Instituto de Investigación Biosanitaria de Granada, Faculty of Health Sciences, University of Granada, Spain.*

Background. Fibromyalgia (FM) is a syndrome characterized by chronic widespread musculoskeletal pain with aetiology unknown. New researches highlight the existence of peripheral blood circulation disorders established by changes in innervation to the arterio-venous anastomoses (AVAs) located in the hypothenar eminence of the hands, influencing the vascular system of the human body which would explain the diffuse pain in FM patients.

Objectives. To analyse the peripheral vascular blood flow at skin surface of the hypothenar eminence of the hands and its relationship with pressure pain thresholds (PPTs) in FMS patients.

Methods. A total of 30 women diagnosed with FM and 30 healthy women were enrolled in this case-control study. The hypothenar eminence temperature of both hands with infrared thermography camera (FLIR Systems, INC., USA) and PPTs (digital pressure algometer device) were measured. Linear regression analyses were conducted to determine the associations among the hypothenar eminence temperature of the hands and PPTs.

Results. Linear analysis regression revealed significant associations between hypothenar eminence temperature of both hands and supraspinatus dominant [β=0.647, 95%CI=(0.005, 1.289), p=0.049], greater trochanter dominant [β=0.567, 95%CI=(0.1.34, 1.000), p=0.013], greater trochanter non dominant [β=0.542, 95%CI=(0.082, 1.003), p=0.023], and anterior tibial dominant [β=0.026, 95%CI=(0.063, 0.904), p=0.026] PPTs after adjustment for age, BMI, and menopause status. No significant associations were found for healthy women.

Conclusions. Our findings showed that women with FM present an association between hypothenar eminence temperature of the hands and pain levels such as the tenderness over some points of musculoskeletal system.

O-04

DIAGNOSIS OF FIBROMYALGIA: COMPARISON OF AAPT AND ACR CRITERIA

Marco Antivalle, Federica Rigamonti, Michele Agosti, Valeria Giorgi, Piercarlo Sarzi-Puttini
Rheumatology Unit, L. Sacco University Hospital, Italy.

Background/Purpose. In recent years, the diagnostic criteria for fibromyalgia (FM) have been reviewed multiple times, up to the publication of the provisional criteria of the ACR in their 2016 revision (1). In 2018, a revised FM diagnosis was proposed by the ACTION-APS Pain Taxonomy (AAPT) (2), requiring for the diagnosis the presence of multisite pain (MSP), defined as 6 or more painful sites of a total of 9 possible sites, plus moderate to severe sleep problems or fatigue. The purpose of this work was to compare the diagnostic characteristics of the different sets of criteria.

Methods. The study population consisted of 530 patients (481 F, 49 M, mean age 47.9±11.7 yrs) referred for fibromyalgia. All patients underwent a complete clinical workout, including the compilation of multiple questionnaires addressing the different domains of fibromyalgia. All patients were classified according to the newly proposed criteria and to the different sets of ACR criteria, including the 1990 criteria based only on tender points count, and the revised 2010 criteria with 2011 and 2016 revisions. Statistical analysis were performed with SPSS software, and parametric and nonparametric methods were used as appropriate.

Results. Overall, FM was diagnosed in 95% of patients (503/530) by AAPT criteria; for ACR criteria, a diagnosis of FM was made in 79% (420/530), 92% (488/539), 91% (482/530), and 71% (374/530) respectively by 2016, 2011, 2010 and 1990 criteria (Figure 1). The overall agreement (k statistics) between AAPT and the four sets of ACR criteria, although statistically significant p 0.001 in all cases), was at best moderate (0.120, 0.472, 0.428, and 0.324 respectively). In particular, comparing AAPT and ACR2016 criteria, there were 89 discrepant cases, mostly diagnoses of FM by AAPT not confirmed by ACR2016 criteria (AAPT+/ACR2016-, N=83; AAPT-/ACR2016+, N=6). Overall, AAPT+/ACR2016- cases showed a moderate pain level (average 5.89±2.4 on a 0-10 NRS scale) and 82% was characterized by mild to moderate severity according to Polysymptomatic Distress Scale (value 12).

Conclusions. Our results confirm that the diagnosis of fibromyalgia by the newly proposed AAPT diagnostic criteria is not completely coincident with ACR criteria. Fibromyalgia will be diagnosed more frequently by the new criteria. Further analysis is necessary to fully clarify the real extent of the proposed changes.

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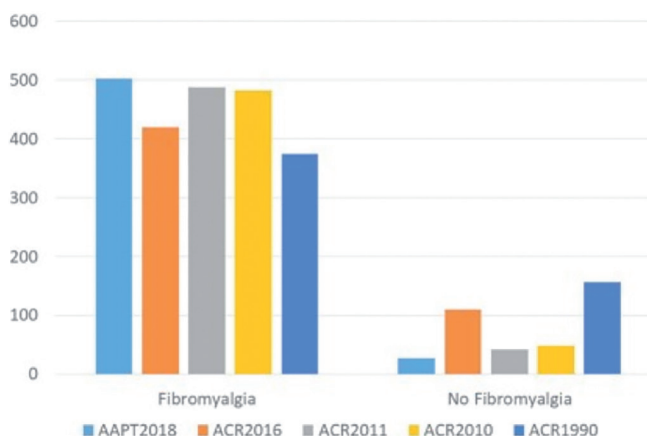

Fig. 1. Classification of 530 patients according to the different sets of criteria.

O-05

ALTERED SUBPROCESSES OF WORKING MEMORY IN FIBROMYALGIA PATIENTS: AN ERP STUDY USING N-BACK TASK

Francisco Mercado, David Ferrera, Roberto Fernandes, Irene Peláez, Alberto Carpio, María Eugenia De La Hoz, Paloma Barjola
Psychology, Rey Juan Carlos University, Spain.

Objectives. Cognitive dysfunction in fibromyalgia has become a key symptom considered by patients as more disabling than pain itself. Experimental evidence from neuropsychological and neuroimaging studies points out that such cognitive impairments are especially robust when patients need to set in motion working memory processes, suggesting the existence of an altered functioning underlying neural network involving both the prefrontal and parietal regions. However, the temporal dynamics of working memory subprocesses have not yet been explored in fibromyalgia.
Subjects. Thirty-six right-handed women took part in the experiment: eighteen fibromyalgia patients and eighteen healthy controls.
Methods. Event-related potentials and behavioural responses were recorded while participants were engaged in a 2-back working memory task. Principal Component Analyses were used to define and quantify ERP components associated with working memory processes.
Results. Patients with fibromyalgia exhibited worse performances than the control group as revealed by their number of errors in the working memory task. Moreover, both scalp right parieto-occipital P2 and left parietal P3 amplitudes were lower for fibromyalgia patients than for healthy control participants. Regression analyses revealed that lower P3 amplitudes were observed in fibromyalgia patients reporting higher pain ratings.
Conclusions. Neural indices and behavioural performance suggest that encoding of information and, subsequently, context updating and the replacement, as a part of working memory subprocesses, are impaired in fibromyalgia patients. Studying the temporal dynamics of working memory by ERP methodology is a useful approach to detect specific cognitive impaired mechanisms in fibromyalgia. It could use to develop more adjusted treatments to each patient.

O-06

ANALGESIC EFFECT OF IV MAGNESIUM ASPARTATE IN FIBROMYALGIA: A DOUBLE-BLIND PLACEBO CONTROLLED STUDY

Greta Moorkens, Jela Illegems
General Internal Medicine, Antwerp University Hospital, Belgium.

Background. The blocking action of magnesium on N-methyl-D-asparagine acid receptors, involved in pain conduction was used in the hypothesis that administration of magnesium could cause pain relief in Fibromyalgia patients.
Objectives. to evaluate the analgesic effect of IV magnesium aspartate in a double-blind placebo controlled setting
Methods. 15 female fibromyalgia (ACR criteria 2010) patients were included, randomly assigned into one of three IV administration schemes in the short stay hospital unit with: scheme 1 (magnesium-placebo-magnesium), scheme 2 (placebo-magnesium-magnesium) and scheme 3 (magnesium-magnesium-placebo). Interval between 2 IV administrations was 14 days. On 6 well defined moments (interval 1 week) every patient filled out four assessment scales: The multidimensional pain inventory (MPI), oswestry disability index (ODI), hospital anxiety and depression scale (HADS) and the visual analogue scale (VAS). For statistical analysis IBM SPSS Statistics version 25 was used.
Results. After two consecutive IV magnesium administrations (scheme 3) the VAS score showed the lowest value, however no statistical significance was reached. After administration of placebo, VAS and MPI showed higher scores without statistical significance.
Conclusions. The study sample was to low to jump conclusions on the analgesic effect of IV magnesium aspartate in fibromyalgia. Further research is recommended.

O-07

MU-LYMPHO-MARKER: A BIOLOGICAL MARKERS FOR CHRONIC PAIN DIAGNOSIS: FIRST IDENTIFICATION OF MU-LYMPHOCYTIC-MARKER IN PATIENTS AFFECTED BY FIBROMYALGIA AND OSTEOARTHRITIS

William Raffaeli[1], Valentina Malafoglia[1], Antonello Bonci[1,2], Michael Tenti[1], Paola Gremigni[3], Sara Ilari[4], Laura Vitiello[5], Cristina Iannucelli[6], Chiara Gioia[6], Manuela Di Franco[6], Tomino Carlo, Carolina Muscoli[4].
[1]*Institute for Research on Pain, ISAL Foundation, Italy;*
[2]*Global Institute on Addictions, USA;*
[3]*Dept. of Psychology, University of Bologna, Italy;*
[4]*Institute of Research for Food Safety & Health (IRC_FSH), Department of Health Sciences, University 'Magna Graecia' of Catanzaro, Italy;*
[5]*Unit of Flow Cytometry, IRCCS San Raffaele Pisana, Italy;*
[6]*Rheumatology Unit, Dept of Internal Medicine and medical Specialties Sapienza University of Rome, Italy.*

Background and objectives. Fibromyalgia (FM) is one of the most disabling chronic pain syndromes, with a prevalence between 0.2 and 6.6% worldwide, affecting above all middle-aged women. FM main symptoms, in addition to chronic pain, include sleep disturbances, chronic fatigue, cognitive dysfunctions and other somatic symptoms. Moreover, FM is associated with anxiety, stress-related symptoms and depression. The ACR criteria for FM diagnosis have changed over time (Wolfe *et al.*, 1990; Wolfe *et al.*, 2010 / 2011 and 2016), maintaining advantages and limitations (Sarzi-Puttini *et al.*, 2018) and clinicians rely only on clinical examination and questionnaire administration to make a diagnosis (Hauser and Fitzcharles, 2018). Recently, FM has been recognized as a pathological condition, characterized by chronic primary pain, which could be assimilated as a disease in its own right. However, FM patients are frequently labeled with a "somatoform pain disorder" or "affective disorder" diagnosis. FM lacks, as any chronic pain disease, of specific diagnostic biomarkers; neither specific diagnostic laboratory tests nor biomarkers are available to confirm FM diagnosis. In this context, delays and misdiagnosis may frequently occur, with relevant consequences on patients' life and treatment efficacy, as well as socioeconomic burden on both patients and health care systems (Choy *et al.*, 2010; Di Franco *et al.*, 2011; Ghavidel-Parsa *et al.*, 2015; Walittet *al.*, 2015; Mengshoelet *al.*, 2018 Hauser *et al.*, 2019). For these reasons, the identification of objective and specific FM and Chronic Pain biomarkers is a priority for a correct diagnosis. Interestingly, endogenous opioid system is close to the immune one because of the expression of opioid receptors on lymphocytes membrane. Here we analyzed the role of Mu opioid receptor on B lymphocytes membrane, as specific biomarker for FM and osteoarthritis (OA) patients.
Methods. Three groups of patients were enrolled: FM, chronic pain OA (positive control group) and pain-free healthy (negative control group) subjects. We collected blood samples in order to apply immunophenotyping analysis and detect the percentage of opioid receptors on the surface of different cells populations. All patients attended psychological tests. Data were statistically analyzed.
Results. Final results showed that the percentage of Mu-positive B cells were statistically lower in FM and OA patients than in pain-free subjects: considering the intensity of pain expressed as numerical rating scale (NRS), FM or OA patients with moderate/severe intensity of pain presented a lower percentage of B cells expressing Mu opioid receptor than patients in pain free control group. Patients with a mild pain sensation showed a percentage of Mu-positive B lymphocytes not significantly different from the pain free control group. Moreover, we showed that FM and OA patients suffering for less than five years expressed a Mu-positive B cells percentage significantly lower than patients suffering for more than five years. We found that, despite the different pharmacological therapies, the percentage of Mu receptor on B cells was almost identical across the subgroups.
Overall, our results indicate that a lower Mu opioid receptor expression on B cells corresponds to a greater impact of FM and to a perception of having a syndrome with chronic duration and serious consequences on one's life.
Conclusions. Here we identified Mu opioid receptor, expressed on B lymphocytes surface as a biological marker, named Mu-Lympho-Marker, for an objective chronic pain diagnosis for FM and OA patients. Moreover, we described FM as a truly painful disease. In particular, we certified that FM pain perception is an objective widespread chronic pain status that have characteristic similar to a nociceptive pain due to ostheoarthritic disease.
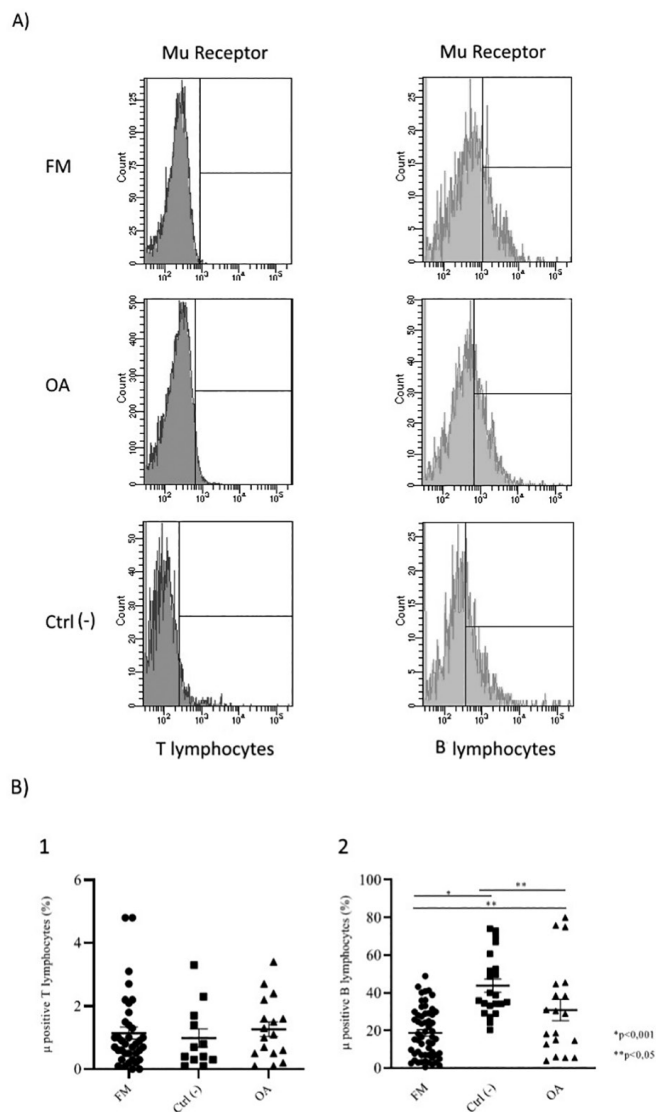
Fig. 1. A) Flow cytometry analysis of Mu opioid receptor in FM, OA e CTRL- patients in T lymphocytes and **B** lymphocytes. B) Mu+ T cells percentage (1) and Mu+ B cell percentage (2) in FM, OA, CTRL- patients groups.

O-08

FIBROMYALGIA AS A COMORBIDITY IN CONNECTIVE TISSUE DISEASES: IMPLICATIONS FOR QUALITY OF LIFE AND DISEASE ACTIVITY ASSESSMENT

Jan Toms, Tomas Soukup, Petr Bradna
2nd Dep. of Internal Medicine, Faculty of Medicine and University Hospital Hradec Kralove, Czech Republic.

Background. Fibromyalgia (FM) has been well documented to accompany frequently connective tissue diseases (CTD). Much less data are available concerning differencies in FM impact on individual CTD.
Objectives. To compare the impact of concomitant FM on CTD in terms of pain intensity, disease activity, function disability and quality of life (QOL) in a regional, monocentric, cross-sectional study.
Methods. 120 consecutive patients (pts) with rheumatoid arthritis (RA), 91 pts with systemic lupus (SLE), 30 pts with inflammatory myopathy (IM) and 30 pts with systemic sclerosis (SSc) were examined in the outpatient rheumatology department on the presence of FM (criteria ACR/1990).

Standard Manual Tender Point Survey was used for the examination of FM tender points. The following data were recorded: demographic data, tender point count (TPC), pain, fatigue and stiffness intensity on a 100 mm visual analog scale (VAS), Fibromyalgia Impact Questionnarie (FIQ) score and disease activity parameters according to individual CTD representatives. Health Assessment Questionnarie (HAQ) and Short Form 36 items (SF-36) were used for evaluation of functional disability and QOL, respectively. Statistical analysis was based on Kruskal-Wallis nonparametric tests comparing mutually all the CTD cohorts with and without FM. Patient file with SSc and FM was not included into the analysis due to small quantity.
Results. FM was classified in 25 (20.8%) pts with RA, 10 (11.0%) pts with SLE, 4 (13.3%) pts with PM/DM and 1 patient with SSc (3.3%). CTD groups with concomitant FM were shown to have significantly higher levels of pain, fatigue, stiffness, TPC and FIQ (*p* 0.05). RA/FM pts reached the highest average intensity of pain (VAS pain 63.7 mm), the worst disability level (HAQ 1.83) and the most reduced QOL in some of SF-36 domains. Disease activity assessment was significantly influenced only in RA (*p*=0.0001), RA/FM pts reached much less frequently remission based on composite indices (DAS-28, CDAI, SDAI) in comparison to RA without FM.
Conclusions. FM occurs as a comorbidity most frequently in pts with RA in comparison to other CTD. RA patients are also mostly influenced by FM at the level of pain perception, disability and QOL. This FM impact contributes to significant difficulties in RA disease activity assessment unlike other CTD.

O-09

CATASTROPHIZING, ACCEPTANCE, AND SELF-EFFICACY AS MEDIATORS BETWEEN PAIN AND DISABILITY IN FIBROMYALGIA

Giorgia Varallo
Psychology, Catholic University of Sacred Heart, Italy.

Background. Research has shown that catastrophizing, acceptance, and pain self-efficacy have an important predictive role in chronic pain, but it's not exactly known how these cognitive variables influence the adjustment to pain in a fibromyalgia (FM) population. The main aim of this study is to explore the relationship between pain, emotional distress, and impairment in FM patients, considering the potential mediating role of pain catastrophizing, pain acceptance and pain self-efficacy; the second objective is to compare FM patients and rheumatoid arthritis (RA) patients in order to explore potential differences in the cognitive appraisal of pain.
Objectives. This cross-sectional study examine the following specific hypothesis: (1) FM patients will report greater pain, emotional distress, and pain-catastrophizing, less acceptance of pain experience and pain self-efficacy than rheumatoid arthritis (RA) group; (2) FM patients will show a significant correlation between pain, catastrophizing, acceptance, pain self-efficacy, emotional distress, and disability; (3) in FM patients, the relationship between pain and emotional distress and disability will be mediated by the appraisal of pain as threatening (catastrophizing), the openness to the experience of pain (acceptance) and the perceived pain self-efficacy.
Methods. Twenty FM patients and twenty participant controls were evaluated on pain and psychological-related variables using the following measures:
- Pain Catastrophizing Scale
- Pain Self-efficacy Questionnaire
- Chronic Pain Acceptance Questionnaire
- Hospital Anxiety and Depression Scale
- Brief Pain Inventory
- Numeric Rating Scale
- Fibromyalgia Impact Questionnaire
Results. Preliminary results underline that pain catastrophizing, pain acceptance and pain self-efficacy are significantly correlated with emotional distress and/or disability. Catastrophizing has a significant effect as a mediator on the relationship between pain and emotional distress and also with disability.
Conclusions. FM patients are likely to benefit from interventions that address psychological variables such as pain catastrophizing. The current management of FM could improve by providing cognitive techniques aimed at modifying the negative appraisal of pain.

P-01

IL-6 CYTOKINE LEVEL: RELEVANCE TO INFLAMMATION INDUCED PAIN AND FATIGUE IN FIBROMYALGIA AND ME/CFS

Marisa L Amato[1], Kristy Themelis[1], Beth Thompson[2], Robyn Stocks[2], Amy Pound[1], Zdenka C Cipinova[4], Lorraine Shah-Goodwin[4], Jean Timeyin[4], Andrew Barrit[3], Hugo D Critchley[1], Kevin A Davies[2], Neil A Harrison[5], Jessica A Eccles[1]
[1]Neuroscience, Brighton and Sussex Medical School, UK;
[2]Medicine, Brighton and Sussex Medical School, UK;
[3]Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, UK;
[4]Clinical Investigation & Research Unit (CIRU), Brighton and Sussex University Hospitals NHS Trust, UK;
[5]Immunopsychiatry Research Group, Cardiff University Brain Research Imaging Centre, UK.

Introduction. Fibromyalgia and ME/CFS are chronic, disabling, often poorly understood conditions, with overlapping systemic physical and psychological symptoms. Inflammatory abnormalities are reported. We seek to clarify how inflammation contributes to pain and fatigue in these conditions.
Methods. Seventy-seven participants (Clinical Diagnoses of Fibromyalgia or ME/CFS or both (n=53) and healthy controls (n=24)) -- were tested under two randomised conditions on separate visits: Inflammatory state (following typhoid vaccine) or placebo (following saline injection). IL-6, pain (VAS, Pressure Pain Thresholds, (PPT)) reported fatigue (VAS).
IL-6 levels were determined by High Sensitivity ELISA and analysed as absolute values, and as log values due to distribution of values.
Associations were tested using regression, correcting for BMI as appropriate.
Results. Across all participants baseline IL-6 concentration significantly correlated with baseline pain score (r=0.345, n=77, p=0.002) and reduction in PPT after vaccination on thumb (r= -0.577, df=10, p=0.05, corrected) and hypothenar eminence (r= -0.744, df=10, p=0.006, corrected).
IL6 concentration post-vaccination significantly correlated with baseline pain (r=0.240, n=77, p=0.036).
Inflammation-induced change (placebo controlled) in IL6 correlated with both change in self-reported physical fatigue (r=0.609, df=10, p=0.036, corrected) and self-reported pain (r=0.675, df=10, p=0.016, corrected) induced by inflammation challenges.
Discussion. These results demonstrate a relationship between inflammation, pain, fatigue in Fibromyalgia and ME/CFS, previously poorly characterized.
Conclusions. Ongoing research is investigating these relationships in Fibromyalgia and ME/CFS including neuroimaging and transcriptomics. Understanding these biological mechanisms is crucial for targeting future therapeutic interventions and diagnostics in a patient group with significant morbidity.

P-02

INFLAMMATION INDUCED DIFFERENCES OF INTERLEUKINE-6 (IL6) CONCENTRATION IN FIBROMYALGIA AND ME/CFS

Marisa L Amato[1], Kristy Themelis[1], Beth Thompson[3], Robyn Stocks[3], Amy Pound[1], Zdenka C Cipinova[4], Lorraine Shah-Goodwin[4], Jean Timeyin[4], Andrew Barrit[2], Hugo D Critchley[1], Kevin A Davies[3], Neil A Harrison[5], Jessica A Eccles[1]
[1]Neuroscience, Brighton and Sussex Medical, UK;
[2]Clinical Imaging Sciences Centre, Brighton and Sussex Medical, UK;
[3]Medicine, Brighton and Sussex Medical, UK;
[4]Clinical Investigation & Research Unit (CIRU), Brighton and Sussex University Hospitals NHS Trust, UK;
[5]Immunopsychiatry Research Group, Cardiff University Brain Research Imaging Centre, UK.

Introduction. Fibromyalgia and ME/CFS are chronic, disabling, often poorly understood conditions, with overlapping systemic physical and psychological symptoms. Inflammatory abnormalities are reported, including differences in baseline cytokines, with conflicting results. To our knowledge change in IL6 in response to typhoid vaccination as an inflammatory challenge in this patient population has not yet been reported.
Methods. Seventy-seven participants (Clinical Diagnoses of Fibromyalgia

or ME/CFS or both (n=53) and healthy controls (n=24)) -- were tested under an inflammatory challenge - two randomised conditions on separate visits: Inflammatory state (following typhoid vaccine) or placebo (following saline injection). IL-6 concentration was measured pre and post (4 hours) injection.
IL-6 levels were determined by High Sensitivity ELISA and analysed as log values due to distribution of values.
Associations were tested using repeated measures ANOVA and regression correcting for BMI as appropriate
Results. There is a significant difference in baseline log IL6 concentration between patients and healthy controls (p=0.002). However, baseline log IL6 is significantly associated with BMI (p 0.001). BMI differed significantly between the two groups with higher BMI in patients compared to controls (p=0.012). After analyses correcting for BMI correction, the group difference in baseline log IL6 is rendered non-significant.
Across the whole group of study participants, typhoid vaccination induced a significant change in log IL6 compared to placebo (p 0.001). However, there were no significant group differences between patients and controls, with and without controlling for BMI.
Discussion. These results demonstrate a relationship between BMI and IL6 concentration, which may be a confounder in similar studies. Inducing inflammation with typhoid vaccination increases the IL6 level, but our evidence does not support a direct relationship between the induced change in IL6 and Fibromyalgia and ME/CFS. However, non-IL6 mediated inflammation may be an important factor in these conditions.
Conclusions. Further investigation related to neuro and peripheral response to inflammation including neuroimaging, precise transcriptomic analyses and characterisation of individual differences may inform the role inflammation has in these conditions and support future treatment targets.

P-03

FIBROMIAL FORTE: A NUTRACEUTICAL PRODUCT IN THE TREATMENT OF FIBROMYALGIA

E. Battisti, A. Albanese, F. Filippi
Siena University, Italy.

Background. Fibromyalgia predominantly affects women with myalgia, sleep disorders, asthenia, anxiety and depression. There are not any specific diagnostic tests or therapies, although antidepressants, antiepileptics and analgesics are used. The aim of this study is to evaluate a nutraceutical product with boswellia, carnitine, alpha-lipoic acid (FIBROMIAL FORTE) in the treatment of Fibromyalgia.
Tools and Methodologies. The sample included 60 women suffering from Fibromyalgia who have been divided in 3 groups, by ACR criteria. All of them were asked to complete a test with the Visual Analog Scale (VAS) and Revised Fibromyalgia Impact Questionnaire (R-FIQ). Tests were conducted on day 1, day 30 and 60.
The first group was taking Pregabalin 75mg 2cp/die on the first month, then 150mg 2cp/die on the second month. The second group was taking Tramadol 37,5 mg + Paracetamol 325mg 3cp/die for 2 months. The third group was taking FIBROMIAL FORTE 3cp/die for 2 months. Every subject was doing physical activity 20 minutes per day.
Results. After 30 days, no patient from the first group was showing any improvement. Therefore, painkillers were administered to all of them.
After 60 days, 10 of them were showing improvement in terms of pain and R-FIQ indexes. Finally, 16 of them experienced dizziness and drowsiness.
In the second group, only 2 patients showed improvement after 30 days; however, after 60 days, 13 subjects showed progress in terms of pain and R-FIQ indexes.
After 30 days, 6 patients from the third group were getting better in terms of pain. After 60 days, a total of 17 subjects experienced progress in terms of pain and R-FIQ indexes.
Conclusions. Fibromyalgia is a complex pathology whose therapy is not univocal. Drugs with possible side effects are associated with physical and cognitive-behavioural therapies. In this study, we aimed at evaluating a supplement containing boswellia, carnitine and alpha-lipoic acid in the treatment of Fibromyalgia. Results show that FIBROMIAL FORTE is effective in reducing pain and in improving motor functions, without side effects.
Additional studies will confirm its validity and tolerability for those patients not responding to current therapies.

P-04

NUTRITIONAL INTERVENTION IN PATIENTS WITH FIBROMYALGIA IMPROVED THEIR INTESTINAL PERMEABILITY, SYMPTOMS AND QUALITY OF LIFE

Francisco José Berral[1], Paola Zambrano[2], José Luis Pareja[3],
Genoveva Berná[4], Francisco Martín[4], Manuel Blanco[2], Oscar Cáceres[2]
[1]Department of Sport and Informatic, University Pablo Olavide, Spain;
[2]SHC Unit, Hospital Santa Ángela de la Cruz, Spain;
[3]School of Sciences, Universidad Mayor, Chile;
[4]Department of Molecular Biology and Biochemistry Engineering, University Pablo Olavide, Spain.

Background. Increased intestinal permeability (IP) may have pathogenetic relevance in fibromyalgia (FM) because it leads to the exposure of immune cells to luminal antigens and consequent immune modulation. In addition, FM patients´ experience food sensitivities that aggravate their symptoms and quality of life. Unfortunately, there is not a comprehensive list of foods that may trigger symptoms.
Objectives. To evaluate IP, FM symptoms and quality of life, in patients, as primary efficacy variable, after 6 months of nutritional intervention.
Methods. Patients with FM (80% female-20% male) were included in a randomized, controlled, unicenter longitudinal 6 months nutritional intervention study: i) Medicated patients (n=86; 57.5±1.3 y) without nutritional intervention and ii) Medicated patients following a nutritional intervention (n=139; 55±0.7 y). The diagnosis of FM was made in accordance with the ACR criteria. IP was assessed measuring by ELISA lipopolysaccharide, zonulin and ab-anti-β-lactoglobulin. Direct basophil degranulation test incubating patients´ blood with different food allergen extracts was used to design nutritional intervention, excluding from the diet those foods inducing basophil degranulation. After the exclusion diet patients were evaluated for IP, FM symptoms and quality of life accordingly to ACR criteria.
Results. Exclusion diet significantly reduced IP (p=0.01) when compared with medicated group. Moreover, the diet significantly reduced (p0.01) WPI, FIQ and SS Scale scores. For all scores, 10% of medicated patients improved 50% and 70% of them did not improve. 80% of patients following the exclusion diet plus medication improved 68% and 10% of them did not improve.
Conclusions. A 6 months exclusion diet for food inducing basophil degranulation improved IP and FM symptoms and quality of life.

P-05

USING EUCLIDEAN GEOMETRY TO IMPROVE FIBROMYALGIA DIAGNOSIS

Francisco José Berral[2], Paola Zambrano[1], José Luis Pareja[3],
Francisco Martín[5], Eugenio Fedriani[4], Oscar Cáceres[1], Manuel Blanco[1]
[1]SHC Unit, Hospital Santa Ángela De La Cruz, Spain;
[2]Department of Sport and Informatic, University Pablo Olavide, Spain;
[3]School of Sciences, Universidad Mayor, Chile;
[4]Department of Economy, Quantitative Methods and Economic History, University Pablo Olavide, Spain;
[5]Department of Molecular Biology and Biochemistry Engineering, University Pablo Olavide, Spain.

Background. There have been many efforts to improve the identification of patients with fibromyalgia (FM). The diagnosis criteria have been reviewed in several occasions and they try to be useful for clinical practice, not to lose patients and to deal with the fact that FM is a multi-symptom disorder. Thus, it is important to devise a new core criterion for a simpler FM diagnosis.
Objectives. To improve FM diagnostic criteria based on mathematical analysis establishing only a core set of diagnostic symptoms.
Methods. A cohort of patients diagnosed with FM, from 2008 to 2019 (n=4,989; 88% female-12% male; 62.3±1.1 years; 18-80 years) was used. The patient database includes demographic, clinical, laboratory and medication prescription data. All patients were diagnosed with FM in accordance with the ACR criteria, using the WPI, FIQ and SS Scale scores, by specialists of the FM Unit of Santa Angela de la Cruz Hospital. Firstly, descriptive statistical analyses where performed to test normality, randomness and correlation. Then, a technique based on Euclidean geometry was used.
Results. The three variables (WPI, FIQ and SS Scale scores) did not pass the Kolmogorov-Smirnov normality and randomness tests. The bivariate

correlations showed a direct and moderated lineal relationship between all combinations of two possible variables. When comparing, individually, the three variables with their sum information is lost. The calculation of the hyperplane with the median of the three variables established a pain threshold that allowed us to calculate each patient's condition.
Conclusions. We have identified a one-dimensional measure based in the implementation of a hyperplane that represents the pain threshold.

P-06

"I USED TO BE A VERY ACTIVE PERSON. NOT ANYMORE": FUNCTIONAL DISABILITY IN PATIENTS WITH FIBROMYALGIA. A QUALITATIVE PILOT STUDY IN SPAIN

Erica Briones-Vozmediano[1,2], Mar Patiño-Vera[3], Daniel Sanjuán-Sánchez[1], Carolina Climent-Sanz[1,2], Montserrat Gea-Sánchez[1,2],
Francesc Rubí-Carnacea[1,2]
[1]Department of Nursing and Physiotherapy, University of Lleida, Spain;
[2]Research Group of Health Care (GRECS), Institute of Biomedical Research (IRB), Spain;
[3]Disability Assessment Service, Valencian Government, Spain.

Background. Patients with fibromyalgia experience impairments in body structures (pain, fatigue, sleep disturbances, among others) with a direct functional impact on their daily lives.
Objectives. The objective of this study was to explore fibromyalgia patients' participation in their current environment, understood as their involvement in life situations.
Methods. Exploratory qualitative pilot study based on personal interviews and a focus group, with 12 patients suffering from fibromyalgia (8 women, 4 men) in Spain in 2016. Participants were recruited at hospital fibromyalgia units and patients' associations.
Results. Fibromyalgia patients' daily activities were classified in three categories taking into account the patients' past or current ability to perform them: 1. Previous activities: abandoned tasks (remunerative employment and leisure); 2. Maintained activities, with modifications: when patients use compensatory strategies to being able to continue performing them, such as support products or adaptation of the environment (shower chairs to self-care, peelers to home tasks, adaptation of labour tasks); and 3. New activities: the inclusion of new routines as a result of the diagnosis of fibromyalgia (participating in associative activities, and self-care related with complementary treatments). The capacity to perform or not certain activities have both an economic and social impact.
Conclusions. This study suggests that fibromyalgia patients suffered substantial changes in their capacity, performance of activities and interests as a result of the copying process. To being able to maintain their activity, patients should incorporate adaptations or modifications. Despite fibromyalgia patients' ability and performance of daily activities were mainly restricted, they were increased in new areas (such as associacionism).

P-07

PREDICTORS OF QUALITY OF LIFE IMPROVEMENT IN PATIENTS WITH FIBROMYALGIA TREATED WITH FIB-19-01

Caroline Maindet-Dominici[1], Patrick Kieffert[4], Viviane Chappuis[3],
Mario Barmaki[2]
[1]Centre de la douleur, Centre Hospitalier Universitaire Grenoble Alpes, France;
[2]Douleur et Soins de Support, Clinique Eugene André, France;
[3]Médecine, Centre Hospitalier De Saint Jean De Maurienne, France;
[4]Consultation D'évaluation et de Traitement De La Douleur, Hospital De Mercy, Chr Metz-Thionville, France.

Background. FIB-19-01 is a phytotherapy drug made of several medicinal plants (acerola, ginger, meadowsweet, passionflower, chamomile, quack grass, L-Tyrosine), aimed to propose an alternative to anxiolytics and hypnotics for restoring restful sleep and decreasing fatigue in patients with fibromyalgia syndrome (FMS). In a randomized, controlled trial[1], FIB-19-01 has been demonstrated to improve FMS patients' quality of life (QoL), to decrease fatigue and to reduce mood disturbances.

Objectives. The aim of the present work was to study the predictive factors of QoL improvement, in FMS patients, under real life conditions.
Methods. Patients with FMS (2016 ACR fibromyalgia criteria), were included in a prospective (6 months) multicentre observational study. All received 2 capsules/day of FIB-19-01 for 6 months. Demographics, disease features (symptoms, disease duration, treatments, co-morbidities) and patient self-assessment of QoL (0-10) were obtained at baseline. At month 6, the investigator collected patient`s assessment of QoL improvement (0, 25%, 25-50%, 50%), self-assessment of treatment efficacy, and changes in treatments intake. Predictors of QoL improvement were studied.
Results. 178 patients completed the study. At endpoint, 58% of opioid users had reduced their consumption. 52% of patients had reduced their analgesic consumption. They were 39% for anxiolytics and 35% for hypnotics. 72% of patients reported QoL improvement: 25% in 29% of patients, 25-50% in 47% and 50% in 24%. QoL improvement was correlated with patients' assessment of efficacy (p 0.0001), decrease in use of analgesics (*p* 0.0001), opioids (*p*=0.02) and antidepressants (*p*=0.002), and inversely related to disease duration (*p*=0.02).
Conclusions. QoL improvement was associated with treatment efficacy and treatments decrease. FIB-19-01 might be helpful for reducing conventional therapies and seems more effective in patients with FMS had been evolving for less than one year.

P-08

SLOWLY REPEATED EVOKED PAIN IN FIBROMYALGIA: DIAGNOSTIC ACCURACY PROPERTIES IN COMBINATION TO TYPICAL KEY SYMPTOMS

Pablo de la Coba, Gustavo Reyes del Paso
Psychology, University of Jaén, Spain.

Background. Fibromyalgia is a chronic pain syndrome characterized by central sensitization. We developed a novel slowly repeated evoked pain (SREP) protocol which marker pain sensitization of this condition.
Objectives. To explore the potential improvement in diagnostic accuracy that can be achieved adding SREP to key clinical symptoms of fibromyalgia.
Methods. Clinical pain, fatigue, insomnia, catastrophizing, and negative mood were evaluated in 50 fibromyalgia, 30 rheumatoid arthritis, and 50 healthy individuals. SREP protocol consisted of a series of 9 low intensity painful pressure stimuli of 5s in duration and 30s inter-stimulus interval. Pain was assessed by a visual analogical scale, and SREP was derived by the difference between the last and first ratings.
Results & Discussion. SREP sensitization was observed only in fibromyalgia. Fibromyalgia patients exhibited a more negative psychosocial profile than did rheumatoid arthritis and healthy individuals. SREP was positively correlated with clinical pain, fatigue, insomnia, and catastrophizing, but not with negative mood, in fibromyalgia patients. Singly, SREP discriminated fibromyalgia from rheumatoid arthritis and healthy individuals (85% in both cases). The combination of SREP, fatigue and insomnia allows for an increase in diagnostic accuracy discriminating fibromyalgia from rheumatoid arthritis (86%) and healthy individuals (99%).
Conclusions. Further evidence of SREP as a marker of pain sensitization in fibromyalgia was observed. The combination of this novel dynamic evoked pain index (SREP sensitization) with key clinical fibromyalgia symptoms could improve the diagnosis of this chronic pain condition.

P-09

BODY MASS INDEX, PAIN AND IMPACT OF DISEASE IN WOMEN WITH FIBROMYALGIA

Jamal El Mansouri Yachou[1], María Encarnación Aguilar Ferrándiz[3], Antonio Casas Barragán[1], Rosa María Tapia Haro[1], Francisco Molina Ortega[4], Blanca Rueda Medina[2], María Correa Rodríguez[2]
[1]*Dept. of Physical Therapy, Faculty of Health Sciences, University of Granada, Spain;*
[2]*Dept. of Nursing, Instituto de Investigación Biosanitaria de Granada, Faculty of Health Sciences, University of Granada, Spain;*
[3]*Dept. of Physical Therapy, Instituto de Investigación Biosanitaria de Granada, Faculty of Health Sciences, University of Granada, Spain;*
[4]*Dept. of Health Science, University of Jaén, Spain.*

Background. Fibromyalgia syndrome (FMS) is a chronic disease mainly characterized by widespread pain and associated symptoms including fatigue, cognitive dysfunction, sleep disorders, reduced pain threshold and morning stiffness. Diverse factors like pain sensitivity, reduced physical activity, and mood disorders are linked with body weight in FMS. The relationship between obesity and FMS has not been studied deeply. However, recent studies suggest that chronic pain is associated with higher levels of BMI, which supported the hypothesis that obese people have decreased pain threshold.
Objectives. To evaluate the relationships between body mass index (BMI), global pain, impact of disease and tenderness.
Methods. A total of 73 women with FMS and 73 healthy controls matched on weight and age, were enrolled in this case-control study. BMI were calculated using a body composition analyzer. Global pain was assessed with Visual Analogue Scale (VAS). The Fibromyalgia Impact Questionnaire (FIQ) was used to evaluate the impact of disease and a Digital Pressure Algometer was used to access tender points.
Results. Women with FMS showed significantly higher levels of VAS and TPC in comparison to healthy group (*p* 0.001), but no differences were found between both groups in BMI levels (*p*=0.317). A significant association was observed between FIQ and BMI levels [β(95% CI) = 0.110, (0.010, 0.209), *p*=0.032] after linear regression analysis in women with FMS.
Conclusions. Our results revealed that higher levels of BMI are associated with low scores in FIQ and obese and overweight women with FMS showed higher impact of disease. Furthermore, obese women with FMS have higher pain levels and TPC.

P-10

FIBROMYALGIA 2016 CRITERIA AND ASSESSMENTS: COMPREHENSIVE VALIDATION IN A NORWEGIAN POPULATION

Egil A Fors[1], Knut-Arne Wensaas[2], Hilde Eide[3], Ellen A Jaatun[4], Daniel J Clauw[5,6], Fred Wolfe[7,8], Anne-Sofie Helvik[1]
[1]*Department of Public Health and Nursing, General Practitioner Research Unit, Norwegian University of Science and Technology (NTNU), Faculty of Medicine and Health Sciences, Norway;*
[2]*Research Unit for General Practice, NORCE Norwegian Research Centre, Norway;*
[3]*Science Centre Health and Technology, Faculty of Health and Social Sciences, University of South-Eastern Norway, Norway;*
[4]*St. Olavs Hospital, Trondheim University Hospital, Norwegian University of Science and Technology, Norway;*
[5]*Chronic Pain and Fatigue Research Center, University of Michigan Health System, USA;*
[6]*Department of Anesthesiology, University of Michigan Health System, USA;*
[7]*Forward, the National Data Bank for Rheumatic Diseases, 1035 N. Emporia, Ste 288, USA;*
[8]*School of Medicine, University of Kansas, USA.*

Background. The aim of this study was to translate the fibromyalgia survey questionnaire (FSQ) to Norwegian and validate the 2011 and the 2016 fibromyalgia survey diagnostic criteria (FSDC) against the ACR1990 criteria.
Methods. 120 chronic pain patients formerly diagnosed with fibromyalgia according to the ACR1990 criteria, and 62 controls not diagnosed or wariness of fibromyalgia, were enrolled in this study. All responded to a Norwegian version of the FSQ. The FSQ with the Widespread Pain Index (WPI) and Symptom Severity scale (SSS) subscales, summing up to Fibromyalgia Severity (FS) score, were examined for correlations with the fibromyalgia impact questionnaire (FIQ) and TPCs.

Results. The internal consistency of FS measured by Cronbach's alfa was good (= 0.904). The test-retest reliability measures using intra class correlation were respectable for the FS, including WPI and SSS subscales (0.86, 0.84 and 0.87). FS, WPI and SSS correlated significantly with FIQ (0.74, 0.59 and 0.85) and TPC indicating an adequate convergent validity. The medians of FS, WPI and SSS in the fibromyalgia-group were significantly different from the non-fibromyalgia-group indicating good divergent validity. 2011/2016 FSDC versus ACR 1990 as the gold standard gave a good sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-). The accuracy rate for 2011 and 2016 FSDC were 84%. ROC analysis using FS revealed a very good Area Under the Curve (AUC) = 0.860.
Conclusions. The Norwegian version of FSQ is a valid tool for assessment of fibromyalgia according to the 2011 and 2016 fibromyalgia survey diagnostic criteria (FSDC).

P-11

MINDFULNESS IN FIBROMYALGIA: MEAN LEVELS AND CORRELATION WITH DISEASE BURDEN

Marco Antivalle[1], Federica Rigamonti[1], Michele Agosti[1], Valeria Giorgi[1], Alberto Batticciotto[2], Piercarlo Sarzi-Puttini[1]
[1]*Rheumatology Unit, L. Sacco University Hospital, Italy;*
[2]*Rheumatology Unit, Internal Medicine Department, ASST Settelaghi, Ospedale Di Circolo - Fondazione Macchi, Italy.*

Background. Limited evidence suggests that mindfulness-based interventions can have a role in the management of fibromyalgia (FMS) (1), with positive effects on quality of life, pain perception (2) and sleep problems (3). However, there is little data on the levels of mindfulness in FMS and its relationship with the impact of disease.
Objectives. To evaluate the levels of mindfulness and its correlation with disease burden in FMS.
Methods. Mindfulness was assessed in 112 FMS patients (mean age 45.34±11.36 yrs, 86.5% females) and in 128 (43.60±14.35 yrs, 75% females) healthy control subjects by the Mindful Attention Awareness Scale (MAAS) questionnaire (4). The MAAS, a 15-item scale developed to assess individual differences in the frequency of mindful states over time, is the most popular scale measuring mindfulness. Each item can be scored on a Likert scale from 1 to 6, lower scores indicating a greater tendency towards mindfulness. FMS patients were further evaluated by Widespread Pain Index (WPI) and Symptom Severity Scale Score as per 2016 criteria, by the revised FIQ score, and by the Facit-Fatigue scale. Data analysis, including ANOVA and Pearson correlations, was performed with the SPSS software.
Results. In the whole population, mean MAAS score was 4.17±0.72, a value comparable to literature data in different populations, and was correlated to age (r=0.175, *p*=0.008) but not significantly different in males vs females (4.28±0.67 vs 4.16± 0.72). FMS patients and control subjects showed similar values (4.12±0.80 and 4.22±0.63, *p*=0.291). In FMS patients, the MAAS score showed a significant direct correlation with FACIT-fatigue scores, and a significant inverse correlation with overall impact of disease, as assessed by the burden of somatic symptoms and FIQR score. MAAS score showed no significant correlations with variables directly related to pain domain (WPI, tender points), nor with disease duration.
Conclusions. Mindfulness levels, as assessed by MAAS questionnaire, are not significantly different in FMS patients as compared to unselected healthy control subjects. However, levels of mindfulness are higher in patients reporting a higher disease burden, but lower in patients reporting lower levels of fatigue, and are not significantly correlated to pain.
Mindfulness in FMS shows complex interactions with the different domains of the disease, and needs to be further investigated, in order to clarify its relationship with disease features, and eventually to establish guidelines for mindfulness-based interventions.

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P-12

SUBJECTIVE AGING IN FIBROMYALGIA: WHY DO FIBROMYALGIA PATIENTS FEEL OLD? AN OBSERVATIONAL STUDY

Mehmet Akif Guler, Ebru Yılmaz Yalcınkaya
Physical Medicine and Rehabilitation, Gaziosmanpasa Taksim Training and Research Hospital, Turkey.

Background. Subjective age refers to if an individual experience different from their chronological age. A person can feel older, younger or just the same as their actual age. This symptom and associated factors have not been evaluated in fibromyalgia (FM) patients.
Objectives. The main aim of this study was to compare subjective age rates in FM with healthy controls and to determine the relationship between this felt age and cognitive function, depression, anxiety, sleep quality and fatigue severity of the patients.
Methods. 110 patients diagnosed with FM (91.8% female, 37.3(11) years old) and age and sex-matched 69 healthy controls (91.3% female, 36.5 (11.8) years old) included in the study. Subjective age determined simply asking "How old do you feel?" and the patients divided into 3 groups: Feeling older, same age or feeling younger. Mini-mental state examination, Beck Depression Inventory, Beck Anxiety Inventory, Pittsburgh Sleep Quality Index and Fatigue Severity Scale scores of the patients evaluated. The revised-Fibromyalgia Impact Questionnaire (FIQ-R) applied to FM patients.
Results. 75.5% (n=83) of the FM patients reported "feeling older than their actual age" compared to 13% (n=9) of the healthy controls (*p* 0.001). Subjective age is correlated with fatigue (r=0.539, *p* 0.001), depression (r=0.292, *p* 0.001), anxiety (r=0.286, *p* 0.001), cognitive function (r=-0.416, *p* 0.001) and sleep quality (r=0.397, *p* 0.001) of the patients. Correlation between Total FIQ-R scores and subjective age were significant (r=0.345, *p* 0.001).
Conclusions. Feeling older than their actual age or subjective aging might be an important symptom of the FM. Subjective age of a person is related to fatigue, depression, anxiety, cognitive function and sleep quality and affects quality of life of the patients.

P-13

PILATES OR STRETCHING AS A METHOD TO REDUCE PAIN IN WOMEN WITH FIBROMYALGIA

Juan Pablo Hervas-Perez, Edurne Úbeda-D'Ocasar,
Gracia Gallego-Sendarrubias, Cristina Ojedo-Martín, Mario Caballero-Corella
Physiotherapy, Camilo Jose Cela University, Spain.

Background. Fibromyalgia is a disease of unknown origin; whose etiological hypothesis relates it to a facilitation of mechanisms at the central level (1). The main symptomatology is hyperalgesia at muscular level, accompanied by fatigue and sleep disorders (2). It affects the world population (2-4%) (3), and mainly women. It is characterized by being a sedentary population, with difficulties to perform ADL (4).
Objectives. The objectives of this study were focused on the study of pain behaviour in two intervention groups in women with fibromyalgia and define the behaviour of the pressure pain threshold according to the interventions performed.
Methods. Pilot study, experimental double blind. From a sample of n=17 women, with an age of 54.24±8.98.
We proceed to perform two interventions in two different groups, Pilates (n=7) and Stretching (n=10) for a month to assess how it affects the impact of the disease and pain in patients. Through the statistical program SPSS, the study of the NRS, UDP and TS variables is carried out, combined with the Fibromyalgia Impact Questionnaire (FIQ).
Results. With statistically significant results (*p* 0.05), the Pilates group obtained a decrease in perceived pain at the end of the study, while the Stretching group obtained a decrease in the impact of fibromyalgia.
Conclusions. A four-week Pilates training obtained benefits in reducing pain in patients with fibromyalgia. A stretching training, obtained benefits by reducing the impact of disease and pain, increasing its threshold.
After the results obtained from the present study, we can demonstrate that the therapeutic exercise in women with fibromyalgia reduces its symptoms, and can be a good treatment to combat the disease.

P-14

REDUCTION OF FIBROMYALGIA SYMPTOMS AND IMPROVED PHYSIOLOGIC OUTCOMES AFTER A 6-WEEK INTERDISCIPLINARY PROGRAM

Masoumeh Memarzadeh, Cheryl Hutflesz
Michael G DeGroote Pain Clinic, Hamilton Health Sciences, Canada.

Background. FM is a difficult to treat central sensitization widespread pain syndrome that exists on a continuum. Up to 60% of patients at the Michael G DeGroote Pain Clinic in Hamilton, Ontario, have either a primary or secondary diagnosis of FM. In Ontario, treatment centers that offer multimodal treatment for FM only partially follow international guidelines.
Objectives. Our objective is to measure improvements in patient outcomes following group treatment for FM using international guidelines and validated clinical tools. These tools include FIQR, GAD-7, PHQ-9 and PGIC, 6MWT, TUG, 5 x STS, and grip strength.
Methods. Based on readiness, measured by the Patient Pain Stages of Change Questionnaire, patients attended a 6-week, goal centered program that included evidence-based physiotherapy and psychoeducation. Patients completed assessment tools at admission and discharge, and FIQR, GAD-7, and PHQ-9 again at 3- and 6-month intervals. The paired two-tailed t-test was completed for data analysis.
Results. Over 1 year, 25 patients enrolled in the program, 22 patients completed all questionnaires at admission and discharge, 17 patients at 3 months and 9 patients completed questionnaires at 6 months to date. After 6 weeks of group programming, there were statistically significant improvements in all outcome measures (p0.05). At 3 and 6-month follow-ups improvements in FIQR, GAD-7, and PHQ-9 scores were maintained.
Conclusions. Patients with FM can be successfully treated using multimodal programs that follow international guidelines. The patients' psychological state of readiness to change is a key factor in their participation in programs for successful symptom reduction.

P-15

CLINICAL CHARACTERISTICS, SYMPTOM SEVERITY, AND QUALITY OF LIFE AMONG CHINESE FIBROMYALGIA PATIENTS

Juan Jiao[1], Jing Wang[2], Qiu-Wei Peng[1], Quan Jiang[1]
[1]*Rheumatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China*;
[2]*Clinical evaluation center, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China.*

Objectives. To document the clinical characteristics, fibromyalgia-related symptom severity and quality of life (QOL) among Chinese fibromyalgia patients, and to examine the impact of age on their symptoms.
Methods. Patients meeting the 1990 ACR Research Criteria for fibromyalgia were identified in a tertiary rheumatology clinic population. Each subject volunteer completed a package of validated questionnaires. The patients were further stratified into three groups ("young", ≤39 years; "middle-age", 40-59 years; and "older", ≥60 years) by age for analysis by a covariance model.
Results. One hundred twenty-four sequentially-enrolled fibromyalgia patients were studied. The majority of the recruited patients in this study were women (107, 86.3%) with a mean age of 49.4 years (SD 10.8 years), and a mean FIQ total score of 49.7 (SD 19.1). After stratification on the basis of age, 32 "young" (25.8%), 73 "middle-age" (58.9%), and 19 "older" (15.3%) subjects were further evaluated. The older group exhibited minimal depression, and only mild perceived stress, along with normal sleep quality. By contrast, pairwise comparison among the three-age groups found that the young and middle-age patients were significantly more troubled than the olders by their symptoms in several data categories: FIQ morning tiredness ($Ps≤0.012$), depression ($Ps≤0.002$) and anxiety ($Ps≤0.004$); SF-36 mental health index ($Ps≤0.002$), and their mental component summary ($Ps≤0.017$). The middle-age patients exhibited more trouble than did the olders with SF-36 social functioning ($p=0.008$), role emotional ($p=0.012$), depression (BDI, $p=0.012$), and sleep quality (PSQI, $p=0.017$). The young patients exhibited the highest levels of current experienced stress (Young vs. Old, PSS, $p=0.013$).
Conclusions. This study has identified overall demographic characteristics of Chinese fibromyalgia patients. It is clear, however, that middle-age Chinese fibromyalgia patients exhibited less compromise of their QOL than did their older peers. This discrepancy begs a logical explanation and deserves further study.

P-16

THE PREVALENCE OF COMORBID FIBROMYALGIA SYNDROME WITH RHEUMATIC DISEASES

Przemyslaw Keczmer[1], Grzegorz Rozwadowski[2], Agnieszka Krawczyk-Wasielewska[1], Slawomir Jeka[3], Bogdan Batko[4], Wojciech Romanowski[5], Marek Brzosko[6], Ewa Mojs[7], Wlodzimierz Samborski[1]
[1]*Chair of Rheumatology and Rehabilitation, Poznan University of Medical Sciences, Poland*; [2]*Lower Silesian Rehabilitation Centre, Poland*;
[3]*Clinical Department of Rheumatology and Connective Tissue Diseases, Nicolaus Copernicus University, Collegium Medicum Bydgoszcz, Poland*;
[4]*Rheumatology Clinic, J. Dietl Specialist Hospital, Poland*;
[5]*Reumatological Centre, Poland*;
[6]*Department of Rheumatology Internal Medicine Geriatrics and Immunology, Pomeranian Medical University, Poland*;
[7]*Chair and Dept. of Clinical Psychology, Poznan University of Medical Sciences, Poland.*

Background. Fibromyalgia syndrome (FMS) is one of the most common causes of generalized pain and can occur concomitantly with various rheumatic diseases.
Objectives. The aim of this study was to evaluate the prevalence of FMS in patients with rheumatoid arthritis (RA), spondyloarthritis (SpA) and systemic lupus erythematosus (SLE).
Methods. A total of 285 patients were included in this study. 74 of the patients were male and 231 were female (mean age was 54.68±14.02). 170 RA and 34 SLE patients were diagnosed according to the ACR/EULAR 2010 and SLE SICCA criteria respectively, and 55 patients with spondyloarthritis (23 ankylosing spondylitis and 32 Psoriatic Arthritis) were diagnosed according to the modified New York criteria and CASPAR criteria respectively. A total of 285 participants completed the 2016 fibromyalgia survey questionnaire.
Results. FMS was diagnosed in 22,9% (39 out of 170) RA patients, 21,8% (12 out of 55) SpA group and 20.6% (7 out of 34) SLE patients. The mean levels of fatigue (SLE-FMS 1.78; SLE-nonFMS 1.72, cognitive problems (SLE-FMS 1.03; SLE-nonFMS 0.96) and sleep disturbance (SLE-FMS 1.27, SLE-nonFMS 1.18) were much higher in FMS compared to non FMS patients only in SLE group.
Conclusions. FMS is comorbid in inflammatory rheumatic diseases such as RA, SpA and SLE with prevalence almost at the same level. The level of severity some specific symptoms should be much higher in all FMS groups but it was not observed in this study.

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P-17

TREATING FIBROMYALGIA WITHOUT MEDICATION: A SAFER AND MORE EFFECTIVE APPROACH

Anad Kumar
Clinical, Sales, & Marketing, Electromedical Products International, Inc., USA.

Fibromyalgia is extremely difficult to treat. Medications designed to manage symptoms have limited efficacy and several side effects that further impede a patient's quality of life. Non-pharmacological treatments, to include psychotherapy, allow patients to learn different methods of managing their symptoms and, by extension, moderately improving their quality of life. Alpha-Stim Cranial Electrotherapy Stimulation (CES) devices have been demonstrated in four clinical studies to safely and effectively reduce the symptoms of fibromyalgia, to include pain, anxiety, depression, and insomnia. A total of 209 participants across four studies received CES treatment via electrodes connected to their ears. Treatment was conducted daily for 60 minutes for either three weeks (Cork *et al.*, 2004; Lichtbroun *et al.*, 1999; Lichtbroun *et al.*, 2001) or eight weeks (Taylor *et al.*, 2013). Upon conclusion of treatment, patients in the active treatment groups using reported significantly reduced pain, anxiety, fatigue, and depression when compared to sham groups. Active treatment groups also reported significantly improved quality of life, quality and duration of sleep, and feeling of well-being. Further research into the efficacy of Alpha-Stim devices indicate treatment effects are cumulative and become more effective with repeated treatments (Morriss *et al.*, 2018). Alpha-Stim devices have minimal side effects that are mild and self-limiting.

P-18

FIBROMYALGIA, OBSTRUCTIVE SLEEP APNEA, OBESITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RETROSPECTIVE ANALYSIS

Edwin Meresh, Murali Rao
Department of Psychiatry, Loyola University Medical Center, USA.

Background. Fibromyalgia (FM) patients often have Obstructive Sleep Apnea (OSA), obesity and Attention Deficit Hyperactivity Disorder (ADHD) (1-4) and these could be inter-related. Could there be a common central mechanism linking these overlapping presentations?
Methods. After Institutional Review Board approval for this retrospective chart review, patients diagnosed with FM and co-morbid OSA were identified from an outpatient clinic. The Adult ADHD Self-Report Scale (ASRS-v1.1) symptom checklist (5) available was reviewed and available sleep study results were reviewed. Weight and Body Mass Index (BMI) were abstracted.
Results. FM patients n=34. Mean age: 58±8. 91.2% were female (n=31), mean BMI: 34.7±10.2. Comorbid OSA (n=16, 47.1%), and 69.7% (n=23/33) were obese (BMI 30). Positive ASRS: n=13. FM with positive ASRS, Obesity and OSA diagnosis n=6/13 (46%) (BMI 36.9), (Rapid eye Movement REM sleep duration 43.5 minutes), (REM onset latency 179.7 minutes).
Conclusions. FM, OSA, obesity and ADHD could be related in a sub group of FM patients and decreased REM sleep could play a role (6-8). We have identified a small sub group of FM patients with OSA, obesity and positive ADHD scores in a self-reported scale. Prospective study is needed.

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P-19

FIBROMYALGIA: CLINICAL PATHWAY IN A UNIVERSITY TEACHING HOSPITAL

Veronica Perlo, Federica Laino, Nadia Torchio, Anna De Luca
Pain Management and Palliative Care, Department of Anesthesia, Intensive Care and Emergency, Molinette Hospital, Italy.

Objectives. Fibromyalgia (FM) is a syndrome characterized by widespread chronic musculoskeletal pain often associated with asthenia, sleep disturbances, cognitive, psychological and neurovegetative somatic symptoms. The complexity of this syndrome makes the patient's multidisciplinary management essential, however the lack of a clear diagnostic-therapeutic path often leads to useless medical examinations with consequent delay in diagnosis, increased disability and abuse of health resources.
Our center includes fibromyalgia patients sent by general practitioners and specialists such as rheumatologists and psychiatrists without a validated diagnosis and a well-defined path. In order to improve its management and treatment, we have carried out a review of the current knowledge on fibromyalgia, outlining a diagnostic-therapeutic path that provides for a multidisciplinary approach.
Methods. We examined the epidemiology, pathophysiology and management of FM, through a review of the international literature and carried out an analysis of the diagnostic process that patients faced within our hospital before being sent to our attention. Therefore we developed a specific diagnostic-therapeutic path for these patients.

Results. The application of the path-rules allows us to develop tailored treatment programs according to the clinical features of the various patients. We apply different types of interventions (educational, pharmacological and non-pharmacological) and this behavior reduces useless tests (RX, MRI, blood tests, etc) and diagnostic delays.
Conclusions. Managing FM is long and complex: the entry into our diagnostic-therapeutic path is based on confirmation of diagnosis according to the recent recommendations of the European League Against Rheumatism (2017). The patient evaluation involves several professional figures including psychologist, neurologist and pain therapist and includes neurophysiological tests and investigations to identify also the subgroup of patients with small fiber neuropathy and undertake an individualized program of care.

P-20

FEASIBILITY AND ACCEPTABILITY OF HEART RATE VARIABILITY BIOFEEDBACK AS A TREATMENT FOR THE SYMPTOMS RELATED TO FIBROMYALGIA IN A GROUP OF VETERANS

Marcelaine Reneau
Anesthesia, Ralph H. Johnson, Department of Veterans Affairs Health Center, USA
Nursing, Medical University of South Carolina, USA.

Background. Research suggests autonomic dysfunction and diminished heart rate variability may explain the pain, fatigue, depression, decreased functional status, and poor quality of life (QOL) associated with fibromyalgia (FM).
Objectives. The primary objective was to investigate the feasibility and acceptability of a heart rate variability biofeedback (HRVB) protocol as a nonpharmacological alternative for the treatment of FM. The secondary objective was to investigate a signal of efficacy of improvement of FM-related symptoms.
Methods. Enrolled 10 Veterans for 8 weekly visits of HRVB training on a handheld device and data collection to determine the feasibility to adhere to a recommended HRVB protocol and to examine acceptability and satisfaction with the intervention. Participants were instructed to follow an HRVB protocol of at home practice of twice daily for 20 minutes. Practice frequency and duration data was evaluated for adherence to the treatment protocol. Psychometric data from the Fibromyalgia Impact Questionnaire (FIQR) was evaluated for a signal of efficacy for pain control, functional status, and QOL. A focus group discussion after session 8 examined treatment acceptability and satisfaction.
Results. Data suggest practicing for 20-minutes is feasible (mean time/minutes 19.36), however practicing twice daily is not feasible (mean daily frequency 0.8). Data from the FIQR suggest HRVB contributed to an improvement in functional status and QOL. Veterans reported treatment satisfaction and pain reduction in the focus group session.
Conclusions. Limitations of this study were a small size (n=10) and lack of a control group. Although the prescribed HRVB protocol may not be feasible, a modified HRVB may improve functional status and QOL related to FM. Further studies will focus on a modified HRVB protocol to determine if HRVB can improve functional status and QOL. This study creates the foundation for future studies implementing HRVB as a treatment modality for FM-related symptoms.

P-21

MULTIMODAL APPROACHES FOR FIBROMYALGIA IN INPATIENT CARE: INNOVATIVE COMPLEX TREATMENT COMBINING STUCTURE AND PROCESS QUALITY WITH INCENTIVES

Tobias Romeyke, Elisabeth Noehammer, Harald Stummer
Institute for Management and Economics in Health Care, University of Health Sciences, Medical Informatics and Technology, Austria.

Background. Multimodal treatment approaches tailored to the individual Fibromyalgia patient are recommended and state of the art. This results in high demands on the service providers, who can be financially incentivized to implement innovative and improved care management.
Objectives. The effectiveness of the incentives needs to be evaluated.
Methods. We analyzed quality indicators for multimodal approaches (focus: interdisciplinary treatment for Fibromyalgia) in the German Health Care System according to Donabedian's Trias, just as the pathway entry criteria. Based on data from over 100 hospitals, we compared costs and remuneration for patients with (n=1301) and without multimodal therapy (n=1568), differentiating various cost types.
Results. Multimodal therapeutic approaches for fibromyalgia patients in Germany (1) encompass binding guidelines for the structures and processes in hospitals, (2) incentivize improvements in quality of results and (3) take the higher treatment costs into account.
Conclusions. combining medical, nursing, and therapeutic expertise with binding structures, specified processes, and tools for evaluating results in the sense of Donabedian allows (a) taking individual treatment needs into account while (b) adequately remunerating service providers of Fibromyalgia patients. These findings are highly relevant for designing effective incentive models in health policy and quality management.

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P-22

DAILY FUNCTIONAL COGNITIVE ABILITES AND PARTICIPATION PATTERNS OF WOMEN WITH FIBROMYALGIA

Sara Rosenblum, Priel Buchalter, Eden Twizer, Nuphar Alagem, Inbar Horn
Occupational Therapy, University of Haifa, Israel.

Background. Fibromyalgia is a rheumatic disease mainly frequent among women. The continuous pains accompanied with feasible cognitive decline may set a daily function resilience challenges for those women.
Objectives. This study aim was to evaluate the cognitive abilities as reflected in daily function and participation patterns of women diagnosed with fibromyalgia in comparison to healthy controls.
Methods. Participants were eighty women ages 25-55 who were gathered through social networks. Of them, 40 were diagnosed by a physician as dealing with Fibromyalgia and 40 were healthy age and education matched controls. Women filled in a demographic questionnaire, the Daily Living Questionnaire (DLQ) evaluating cognitive decline as reflected in daily function and Occupational questionnaire (OQ) focusing on daily participation characteristics.
Results. Results indicated significant group differences in cognitive efforts required by women with fibromyalgia to accomplish varied instrumental daily tasks especially those required memory and executive functions. Significant medium correlations were found between the daily cognitive effort and the level of women`s perceived work skill (OQ).
Conclusions. In sum, Fibromyalgia is a disease which challenges woman`s daily function efforts and resilience. As this may cause secondary physical and emotional health complications, more studies are required in order to develop evidence based daily functional interventions for this neglected population.

P-23

PATIENT-REPORTED QUALITY OF LIFE AND INFLAMMATORY BIOMARKERS IN PORTUGUESE PATIENTS OF FIBROMYALGIA - PILOT STUDY

Ana Rita Silva[1,2], Alexandra Bernardo[2], Maria Fernanda Mesquita[2], José Vaz Patto[3], Pedro Moreira[1,4,5], Patrícia Padrão[1,4], Maria Leonor Silva[2]
[1]*Faculdade De Ciências Da Nutrição E Alimentação, Universidade Do Porto, Portugal*;
[2]*Centro De Investigação Interdisciplinar Egas Moniz, Instituto Universitário Egas Moniz, Portugal*;
[3]*Reumatologia, Instituto Português De Reumatologia, Portugal*;
[4]*EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Portugal*;
[5]*Centro de Investigação em Atividade Física, Saúde e Lazer, Universidade do Porto, Portugal.*

Background. It is known that Fibromyalgia (FM) patients experience a poor quality of life (1), along with low grade intestinal inflammation (2).
Objectives. This study aims to characterize pain, fatigue, sleep quality, quality of life and its relation with gastrointestinal symptoms and inflammation in Portuguese FM patients.
Methods. FM patients from *Instituto Português de Reumatologia* were enrolled in this pilot study. The Revised Fibromyalgia Impact Questionnaire (FIQR), Visual Analogue Pain Scale (VAS), Brief Pain Inventory (BPI), Visual Analogue Scale from a list of common gastrointestinal symptoms (VAS_GI), Short Form 36 (SF36), Fatigue Severity Survey (FSS) and Pittsburg Sleep Quality Index (PSQI) questionnaires were applied. Ultrasensitive C Reactive Protein (usCRP) and Erythrocyte Sedimentation Rate (ESR) were quantified. Age, physical activity, anthropometric parameters and bio-impedance measurements were also collected.
Results. Forty-nine FM female patients aged 38 to 71 were evaluated; 75% were overweight/obese. The median usCRP was 0.32 mg/dL, 25% had higher than 0.7 mg/dL, suggestive of low-grade inflammation. The median FIQR score was 59.36 and SF36 35 (physical component: 24.2; mental component: 38.9), reflecting low quality of life. PSQI median was 17 suggesting low sleep quality, and FSS 6.0, reflecting a very tired population. Median VAS was 8.0 and BPI 14.0, indicators of high pain intensity. Regarding GI symptoms, median VAS_GI was 2.6; constipation, flatulence and cramps were reported at least half of the sample.
Conclusions. The study sample was frequently overweight, with severe pain, sleep disturbance, GI disorders and poor quality of life.

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P-24

HYPERMOBILITY PREDICTS DYSAUTONOMIA IN FIBROMYALGIA AND ME/CFS

Bethany Thompson[1], Kristy Themelis[2], Marisa Amato[2], Robyn Stocks[1], Amy Pound[2], Zdenka C. Cipinova[3], Lorraine Shah-Goodwin[3], Jean Timeyin[3], Andrew Barrit[4], Neil A. Harrison[5], Hugo D. Critchley[6], Kevin A. Davies[7], Jessica A. Eccles[2]
[1]*Medicine, Brighton and Sussex Medical School, UK*;
[2]*Neuroscience, Brighton and Sussex Medical School, UK*;
[3]*Clinical Investigation & Research Unit (CIRU), Brighton and Sussex Medical School, UK*;
[4]*Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, UK*;
[5]*Immunopsychiatry Research Group, Cardiff University Brain Research Imaging Centre, UK*;
[6]*Trafford Centre for Medical Research, University of Sussex, UK*;
[7]*Clinical and Experimental Medicine, Brighton and Sussex Medical School, UK.*

Introduction. The pathophysiology of Fibromyalgia and ME/CFS is controversial. Some argue that they are distinct clinical entities but they have overlapping features. Both are known to be independently associated with both dysautonomia (frequently orthostatic intolerance) and variants of connective tissue (hypermobility). This study seeks to explore how hypermobility is related to dysautonomia in Fibromyalgia and ME/CFS compared to healthy controls.
Methods. 73 participants (52 patients with a diagnosis of Fibromyalgia and/

or ME/CFS; 21 healthy controls) underwent assessment of symptomatic hypermobility (2017 hEDS criteria; revised Brighton Criteria for Joint Hypermobility Syndrome (JHS) and underwent an autonomic challenge - active stand protocol.

Results. Current and historical Beighton score were predictive of change in heart rate due to orthostasis (active stand; $p=0.005$; $p=0.002$); with a significant interaction of being a patient on this relationship ($p=0.022$, $p=0.041$) as was hEDS criteria 1 (age and sex adjusted beighton score; $p=0.011$) with a significant interaction of being a patient on this relationship ($p=0.008$). Number of connective tissue features (hEDS criterion 2A) predicted degree of change in heart rate ($p=0.012$), with a significant interaction of being a patient on this relationship ($p=0.038$).

Discussion. Hypermobility is related to orthostatic intolerance in this population and degree of cardiovascular response is predicted by number of connective tissue features. Interestingly this relationship is significantly different in patients versus controls.

Conclusions. Differences between patients and controls in the relationship between hypermobility and dysautonomia highlights the need for further work to scrutinize illness vulnerability models in the pathophysiology of Fibromyalgia and ME/CFS. The association between hypermobility and orthostatic intolerance in this patient group highlights potential personalized treatment targets. Ongoing work explores the relevance of dysautonomia to mechanisms of pain and fatigue.

P-25

SYMPTOMATIC JOINT HYPERMOBILITY: RELEVANCE TO AUTONOMIC-INDUCED PAIN AND FATIGUE IN FIBROMYALGIA AND ME/CFS

Bethany Thompson[1], Kristy Themelis[2], Marisa Amato[2], Robyn Stocks[1], Amy Pound[2], Zdenka C. Cipinova[3], Lorraine Shah-Goodwin[3], Jean Timeyin[3], Andrew Barrit[4], Neil A. Harrison[5], Hugo D. Critchley[6], Kevin A. Davies[7], Jessica A. Eccles[2]

[1]*Undergraduate Medicine, Brighton and Sussex Medical School, UK;*
[2]*Neuroscience, Brighton and Sussex Medical School, UK;*
[3]*Clinical Investigation & Research Unit (CIRU), Brighton and Sussex University Hospitals NHS Trust, UK;*
[4]*Clinical Imaging Sciences Centre, Brighton & Sussex Medical School, UK;*
[5]*Immunopsychiatry Research Group, Cardiff University Brain Research Imaging Centre, UK;*
[6]*Trafford Centre for Medical Research, University of Sussex, UK;*
[7]*Clinical and Experimental Medicine, Brighton and Sussex Medical School, UK.*

Introduction. Fibromyalgia and ME/CFS are disabling, poorly understood conditions. Both are associated with hypermobility -- an indicator of variant connective tissue and both are known to have autonomic and inflammatory abnormalities. We explore how hypermobility relates to autonomic and inflammation mediated pain/fatigue in Fibromyalgia and ME/CFS.

Methods. 65 patients diagnosed with Fibromyalgia and/or ME/CFS and 26 healthy controls were assessed for hypermobility (2017 Criteria for hEDS; Revised Brighton Criteria for Joint Hypermobility Syndrome, JHS) undergoing autonomic challenge (60o head up tilt); a subset underwent an inflammatory challenge (typhoid vaccination) versus placebo (saline injection) on separate randomized counterbalanced visits. Pain and fatigue were assessed.

Results. Meeting Brighton Criteria (JHS) predicted subjective overall, mental and physical fatigue induced by tilt (autonomic challenge) after controlling pre-tilt fatigue ($p=0.009$; $p=0.013$; $p=0.002$). Historical Beighton score correlated with such change in overall and physical fatigue ($p=0.039$, $p=0.01$) hEDS was predictive of placebo-controlled inflammation-induced change in overall subjective fatigue ($p=0.036$) with a significant interaction of being a patient on this relationship ($p=0.037$).

Discussion. These results highlight important relationships between symptomatic connective tissue variants and autonomic and inflammation mediated pain and fatigue in fibromyalgia and ME/CFS. These relationships appear different in patients compared to controls

Conclusions. Understanding these brain-body relationships is crucial for targeting future therapeutic interventions for a population that experience considerable morbidity. Different aspects of hypermobility classification predict different aspects of autonomic and inflammation induced pain and fatigue in Fibromyalgia and ME/CFS.

P-26

IMPLICIT EMOTIONAL PROCESSING IN FIBROMYALGIA: AN EXPERIMENTAL STUDY

Giorgia Varallo[1,2], Federica Scarpina[2], Ada Ghiggia[2,3]
[1]*Psychology, Catholic University of Sacred Heart, Italy;*
[2]*Psychology, Instituto Auxologico Italiano, Italy;*
[3]*Psychology, University of Turin, Italy.*

Background. Aberrant emotional processing is reported in fibromyalgia. However, this capability is generally measured through explicit measures, like self-report measure and facial emotion recognition task. Instead, no previous research has investigated the implicit emotional processing in fibromyalgia.

Methods. Individuals diagnosed with fibromyalgia and matched healthy controls were enrolled. Individuals' capability to recognize the emotions of fear and anger was investigated through an implicit emotional recognition task grounding on the "redundant target effect": people respond faster when two identical targets are presented simultaneously rather than when presented alone. Reaction Times (in ms) and Accuracy (in percentage) were measured. Besides, the level of alexithymia was measured by asking participants to judge explicitly their ability to identify and describe emotions (TAS – 20).

Results. Individuals with fibromyalgia were less accurate and slower in recognizing the emotion of fear when compared to controls. No difference emerged about anger. However, the relationship with the level of alexithymia, when measured using a standard questionnaire was not significant.

Conclusions. Difficulties in the implicit component of emotional processing emerged in fibromyalgia. We discussed our results taking into account the meaning of the emotion of fear in this clinical condition. We also proposed that the individual's capability to efficiently recognize an emotion might be more efficiently inferred studying the implicit behavior, rather than the subjective evaluation of one's emotional processing capability.

P-27

EFFECT OF BRIEF GUIDED IMAGERY ON FEMALE PATIENT DIAGNOSED WITH FIBROMYALGIA - AN EXPLORATORY CONTROLLED TRIAL

Anat Kaplun[1], Tova Rosenbloom[1], Pablo Roitman[2]
[1]*Department of Management, Bar Ilan University, Israel;*
[2]*Outpatient Psychiatric Clinic, Clalit Health Services (CHS), Israel.*

Objectives. To evaluate the effect of Brief Guided Imagery (BGI) on patients suffering chronic, fibromyalgia-related pain.

Background. Fibromyalgia is characterized by chronic pain and accompanied by fatigue, depression, sleep problems, decreased daily functioning, and a lack of energy, thus negatively impacting daily functions, mental and physical health, and quality of life.

Design. An exploratory, controlled trial.

Setting. The study was conducted at Clalit Health Services (CHS) Physiotherapy Institute, Jerusalem, Israel and approved by the CHS IRB (0015-com2-16).

Methods. Thirty-seven female patients diagnosed with fibromyalgia were alternatively allocated to an intervention group 1 (IG1) including 18 patients, or a control group (CG) including 19 patients. Following the first BGI trial, the 16 remaining participants in CG became intervention group 2 (IG2), and 13 patients completed the trial.

Outcome measures. All patients completed a Brief Pain Inventory pain questionnaire and an SF-36 satisfaction questionnaire, before and after the intervention.

Results. The findings of this study are encouraging. Training in BGI was found to be related to significant improvement in pain management, general activity, mood, walking ability, routine work, relationships with others, sleep and enjoyment of life.

Conclusions. We see a trend of improvement following BGI, but more research is needed to investigate this technique. We recommend adding BGI to treatment plans for patients suffering chronic, fibromyalgia-related pain. While other guided imagery methods last up to 20 minutes per session, BGI is innovative since only two minutes are required to obtain a positive effect on chronic pain and quality of life measures.

Author index

A
Ablin Jacob IS-01, IS-20
Achenza Sara IS-18
Agosti Michele O-04, P-11
Aguilar Ferrándiz O-03, P-09
  María Encarnación
Alagem Nuphar P-22
Albanese A. P-03
Aloush Valerie IS-03
Amato Marisa L O-02, P-01, P-02,
  P-24, P-25
Amital Howard IS-16
Antivalle Marco O-04, P-11

B
Banfi Giuseppe IS-06
Baptista Telmo IS-21
Barbic Franca IS-18
Barjola Paloma O-05
Barmaki Mario P-07
Barrit Andrew P-01, P-02, P-24,
  P-25
Batko Bogdan P-16
Batticciotto Alberto IS-23, P-11
Battisti E. P-03
Batty T O-02
Bazzichi Laura IS-15
Berná Genoveva P-04
Bernardo Alexandra P-23
Berral Francisco José P-04, P-05
Blanco Manuel P-04, P-05
Boccassini Laura IS-18
Bonci Antonello O-07
Bradna Petr O-08
Briones-Vozmediano Erica P-06
Brunetta Enrico IS-18
Brzosko Marek P-16
Buchalter Priel P-22
Buskila Dan IS-10

C
Caballero-Corella Mario P-13
Cáceres Oscar P-04, P-05
Cairo Beatrice IS-18
Carlo Tomino O-07
Carpio Alberto O-05
Casale Roberto IS-04, IS-11
Casas Barragán Antonio O-03, P-09
Chappuis Viviane P-07
Cipinova Zdenka C. O-2, P-01, P-02,
  P-24, P-25
Clauw Daniel J. P-10
Climent-Sanz Carolina P-06
Consensi Arianna IS-15
Contreras-Merino Ana M. O-01
Correa Rodríguez María O-03, P-09
Critchley Hugo D. O-02, P-01, P-02,
  P-24, P-25

D
Davies Kevin A. O-02, P-01, P-02,
  P-24, P-25
Davydov Dmitry M. O-01
de la Coba Pablo P-08
De La Hoz María Eugenia O-05
De Luca Anna P-19
Di Carlo Marco IS-17
Di Franco Manuela O-07
Dipaola Franca IS-18

E
Eccles Jessica A. O-02, P-01, P-02,
  P-24, P-25

Eide Hilde P-10
El Mansouri Yachou Jamal O-03, P-09
Elkayam Ori IS-05

F
Fedriani Eugenio P-05
Fernandes Roberto O-05
Ferrera David O-05
Filippi F. P-03
Finn David P. IS-14
Fitzcharles M. IS-08
Folci Marco IS-18
Folgers Stephen IS-12
Fors Egil A P-10
Furlan Raffaello IS-18

G
Gallego-Sendarrubias Gracia P-13
Gea-Sánchez Montserrat P-06
Ghiggia Ada P-26
Giacomelli Camillo IS-15
Gioia Chiara O-07
Giorgi Valeria IS-01, IS-06, IS-22,
  IS-25, O-04, P-11
Gonzalez Barbara IS-21
Gremigni Paola O-07
Guler Mehmet Akif P-12

H
Harrison Neil A. O-02, P-01, P-02,
  P-24, P-25
Häuser Winfried IS-24
Helvik Anne-Sofie P-10
Hervás-Pérez Juan Pablo P-13
Hirche Delia IS-12
Horn Inbar P-22
Hutflesz Cheryl P-14

I
Iannucelli Cristina O-07
Ilari Sara O-07
Illegems Jela O-06

J
Jaatun Ellen A P-10
Jeka Slawomir P-16
Jiang Quan P-15
Jiao Juan P-15
Jones A-M O-02

K
Kaplun Anat P-27
Keczmer Przemyslaw P-16
Kieffert Patrick P-07
Krawczyk-Wasielewska
  Agnieszka P-16
Kumar Anad P-17

L
Laino Federica P-19

M
Maindet-Dominici Caroline P-07
Malafoglia Valentina O-07
Mandelli Pietro IS-18
Martín Francisco P-04, P-05
Mathys Marc G. IS-12
Memarzadeh Masoumeh P-14
Mercado Francisco O-05
Meresh Edwin P-18
Mesquita Maria Fernanda P-23
Mevorach Dror IS-07
Minerbi A. IS-08

Minonzio Maura IS-18
Mojs Ewa P-16
Molina Ortega Francisco O-03, P-09
Moorkens Greta O-06
Moreira Pedro P-23
Muscoli Carolina O-07

N
Noehammer Elisabeth P-21
Novo Rosa IS-21

O
Ojedo-Martín Cristina P-13

P
Padrão Patrícia P-23
Pareja José Luis P-04, P-05
Patiño-Vera Mar P-06
Peláez Irene O-05
Peng Qiu-wei P-15
Perlo Veronica P-19
Porta Alberto IS-18
Pound Amy O-02, P-01, P-02,
  P-24, P-25

R
Raffaeli William O-07
Rao Murali P-18
Reneau Marcelaine P-20
Reyes del Paso Gustavo A. O-01, P-08
Rigamonti Federica O-04, P-11
Roitman Pablo P-27
Romanowski Wojciech P-16
Romeyke Tobias P-21
Rosenbloom Tova P-27
Rosenblum Sara P-22
Rozwadowski Grzegorz P-16
Rubí-Carnacea Francesc P-06
Rueda Medina Blanca P-09

S
Samborski Wlodzimierz P-16
Sanjuán-Sánchez Daniel P-06
Sarzi-Puttini Piercarlo IS-01, IS-15, IS-18,
  IS-25, O-04, P-11
Scarpina Federica P-26
Shah-Goodwin Lorraine O-02, P-01, P-02,
  P-24, P-25
Shiffer Dana IS-18
Shoenfeld Yehuda IS-09
Silva Ana Rita P-23
Silva Maria Leonor P-23
Soukup Tomas O-08
Stocks Robyn O-02, P-01, P-02,
  P-24, P-25
Stummer Harald P-21

T
Tapia Haro Rosa María O-03, P-09
Tenti Michael O-07
Themelis Kristy O-02, P-01, P-02,
  P-24, P-25
Thieme Kati IS-12
Thompson Bethany O-02, P-01, P-02,
  P-24, P-25
Thompson C R O-02
Timeyin Jean O-02, P-01, P-02,
  P-24, P-25
Toms Jan O-08
Torchio Nadia P-19
Torta DM IS-13
Torta Riccardo IS-19
Twizer Eden P-22