WEDNESDAY, 14 JUNE 2017

Fibromyalgia: a disease of the peripheral or central nervous system

SP0019   **SIGNS, SYMPTOMS AND CO-MORBIDITIES OF FIBROMYALGIA**

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In the beta browser version of ICD11, fibromyalgia is listed as a chronic primary pain syndrome (Treede et al. 2015). It is categorized as chronic widespread pain, and is distinguished from other chronic widespread pain by a) tender point counts (American College of Rheumatology 1990 criteria), or b) psychosocial distress (ACR 2010). Both ACR definitions are problematic for research purposes: mechanisms of tender points are poorly understood, and using distress as inclusion criterion may lead to circular arguments.

Chronic primary pain is characterized by significant emotional distress and functional disability. It is multifactorial: biological, psychological and social factors contribute to the pain syndrome. The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms. Chronic Primary Pain can occur in any body site (face, low back, neck, upper limb, thorax, abdominal, pelvis, urogenital region), or in a combination of body sites (Widespread pain). In general, multiple sites of pain are associated with higher distress and disability than single sites. Chronic Primary Pain is also often associated with sleep disturbance, adverse side effects of treatments (such as medication dependence), and comorbidities (such as depression, anxiety, anger, guilt, fear, and a range of chronic medical conditions).

As part of the research consortium LOGIN we have compared the pathophysiology of fibromyalgia, other chronic widespread pain and chronic localized pain in the lower back. In those datasets, fibromyalgia patients showed higher comorbidity of anxiety and depression and more functional impairment than the other groups (Gerhardt et al. 2016). A deficit in conditioned pain modulation (CPM) was related to the spatial spread of ongoing pain, consistent with the neurobiology of endogenous pain control systems. FMS differed from CWP with respect to psychosocial burden, consistent with the shift in clinical diagnostic criteria. Tender point counts (an evoked pain measure) were still useful to identify the FMS patients (Gerhardt et al. 2017). A study using the childhood trauma questionnaire suggests that early stress exposure is associated nonspecifically with lowered pressure pain thresholds which may be related to tender points (Tesarz et al. 2016).

Experimental sleep deprivation in healthy subjects or rodents leads to symptom profiles reminiscent of fibromyalgia (e.g. widespread hyperalgesia, anxiety), suggesting a potential vicious circle of pain, hyperalgesia and sleep disturbance in fibromyalgia.

In summary, fibromyalgia is a chronic primary pain syndrome characterized by widespread pain and major comorbidities. A combination of predisposition plus an initiating painful event seem to play a role in its genesis; according to the dual hit hypothesis, traumatic events during childhood may contribute to the predisposition.

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SP0020   **PERIPHERAL PATHOLOGY IN FIBROMYALGIA**

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The pathophysiology of pain in fibromyalgia is complex. In recent years, an involvement of the thinly myelinated nerve fibers of the A-delta type and the unmyelinated C-fibers has been reported in fibromyalgia patients. Independent research groups have published consistent findings of objective injury to these "small nerve fibers". These included disturbances in function, electrical properties, and morphological integrity of these nerve fibers. While the reasons for this small fiber pathology and its contribution to FMS pain are still unclear, a new research field has emerged that will focus on uncovering the underlying pathophysiology. In this talk, I will summarize current findings and discuss their significance for the understanding of the fibromyalgia syndrome.

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SP0021   **CENTRAL PATHOLOGIES IN FIBROMYALGIA**

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Fibromyalgia is characterized by widespread, mainly muscular pain that is exacerbated during and following physical activity. Although mechanisms such as muscle ischemia and peripheral nerve fibre pathology have been implicated in fibromyalgia, currently no known peripheral pathology can fully account for the pain. Therefore, the pain in fibromyalgia is most likely explained by a complex interaction between peripheral and central mechanisms. Fibromyalgia patients are characterized by a multimodal, widespread, increase in pain sensitivity and a dysfunction of endogenous pain inhibitory mechanisms. Imaging studies have revealed functional as well as structural cerebral abnormalities in fibromyalgia. During painful stimulation, fibromyalgia patients exhibited an inability to activate cerebral structures associated with the descending pain inhibitory system, i.e., rostral anterior cingulate (rACC) and thalamus[1]. There was no association between depression or anxiety and cerebral processing of evoked pain, indicating segregated mechanisms for mood and pain processing[2]. Furthermore, FM patients had less pain related functional connectivity within the brain's pain inhibitory network and structural changes such as decreased cortical thickness and reduced brain volumes[3]. Longer duration of FM pain was associated with more pronounced functional and structural abnormalities suggesting a time-dependent progress of cerebral pathology, even when controlled for age and mood[3]. In addition, FM patients had elevated interleukin-8 in the cerebrospinal fluid indicating neuro-inflammation[4], possibly due to glia cell activation. Interleukin (IL)-8 is co-localized with translocator protein (TSPO) in glia cells. During glia activation, the production of TSPO is increased and TSPO agonists are involved in the regulation of the expression of IL-8 and it's receptor, thus affecting glia to neuron signalling and central sensitisation. We have recently documented that FM patients who are carriers of the genetic functional polymorphism associated with high TSPO binding affinity report higher pain intensity and more severe fibromyalgia symptoms compared to genetically inferred TSPO low affinity binders and that this genetic polymorphism also affects cerebral pain processing[5]. To our knowledge, this is the first finding of genetic mechanisms associated with symptom severity in FM.

Finally, the effect of different treatments on central pathology in FM will be discussed. Short pain duration was predictive of a positive response to a 12 weeks treatment with a serotonin-noradrenalin re-uptake inhibitor (SNRI)[6]. The degree of symptom improvement and reduced pain sensitivity in SNRI treated FM patients corresponded to the degree of increased pain related activation of cerebral areas associated with pain modulation and the default mode network[6]. In contrast, cognitive behaviour therapy did not affect clinical pain or pain sensitivity but increased activations of cerebral regions implicated in executive cognitive control during painful stimulation and thus likely reappraisal of painful stimuli[7]. Finally, 15 weeks of physical exercise partially normalized resting state activity in FM[8]. The results demonstrated that different treatment modalities affected specific brain mechanisms, indicating that at least some of the cerebral abnormalities in FM are reversible.

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Chondrocyte channels (role in mechanotransduction)or "channeling the chondrocyte"

SP0022   **TRPA1 CHANNELS IN OSTEOARTHRITIS**

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Osteoarthritis (OA) has long been viewed as a degenerative "wear-and-tear" disease of cartilage. There is, however, increasing evidence to confirm that inflammation has a critical role in the pathogenesis and symptoms of the disease. Inflammation in osteoarthritis is distinct from that typical for rheumatoid arthritis; it is generally low-grade in its nature but characterized by exacerbations with joint effusions and more severe symptoms. Osteoarthritis shares many features of innate immunity but the inflammatory mechanisms eventually leading to anatomical and functional changes and symptoms typical for osteoarthritis are not known in detail; but their further understanding is essential for the development of disease-modifying treatments for osteoarthritis.

Transient receptor potential ankyrin 1 (TRPA1) is a ligand-gated membrane-bound cation channel. It has been widely studied in sensory neurons where it acts

as a chemosensor for harmful exogenous compounds and mediates pain and neurogenic inflammation. More recently, TRPA1 has been found to be activated also by endogenous compounds formed in inflammation, such as reactive oxygen and nitrogen species. That prompted us to investigate the role of TRPA1 in inflammatory conditions including osteoarthritis.

Monosodium iodoacetate (MIA) -induced arthritis is a widely used animal model of osteoarthritis. We found that MIA evoked acute inflammation, degenerative cartilage changes and joint pain in wild type mice; but interestingly, those responses were significantly attenuated in TRPA1 deficient animals. Furthermore, TRPA1 was found to be expressed and inducible by inflammatory factors including IL-1 and IL-17 in primary human OA chondrocytes; and the TRPA1 channel was shown to be functional based on calcium influx assays. Pharmacological inhibition and genetic depletion of TRPA1 downregulated the production of inflammatory factors and MMP enzymes in mouse cartilage and primary human OA chondrocytes.

The present results introduce TRPA1 as a plausible factor involved in the pathogenesis of OA and provide a novel target for analgesic and anti-inflammatory drugs with disease modifying potential in OA.

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Wearable technologies in 21st century healthcare ——

SP0023 | **REVIEW OF WEARABLE TECHNOLOGIES**

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Working environments have in recent times become less physical with the increase in sedentary, computer-based occupations. Sedentary time is known to be associated with a number of health-related outcomes, including obesity, heart disease, diabetes, cardiometabolic risk factors, some cancers and early mortality, independent of physical activity. There is limited research that has examined sedentary time and physical activity and associations with musculoskeletal conditions, despite these being responsible for the majority of work-related ill health and days absent from work.

The validity and practicality of objective and subjective techniques to measure physical behaviour have been widely reported; however, there is no gold standard that is valid, accurate, reliable and also practical. Self-reported methods can be practical and low-cost, but are subject to recall and social desirability bias; whereas objective devices, such as accelerometers, can be expensive, but allow for information on intensity, frequency and duration of activity to be measured.

The Health Survey for England 2008 used both subjective and objective measures of physical activity: they found that 39% of men and 29% of women were meeting the recommended levels of physical activity when asked via a questionnaire. In comparison, when physical activity was objectively measured using an accelerometer, it was found that only 6% of men and 4% of women met these targets.

Wearable technologies, including research grade accelerometers (e.g. activPAL™) and consumer wearables (e.g. FitBit), are increasingly being used in research, not only to measure physical behaviours but may also be useful in facilitating and monitoring behaviour change. This work will present an overview of wearable technologies used in research, what they can (and can't) measure, and in particular their application in musculoskeletal research.

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SP0024 | **WEARABLE TECHNOLOGIES IN RESEARCH AND CLINICAL TRIALS**

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The use of wearable technology in clinical trials has the potential to be one of the most disruptive innovations in drug development. The cost and duration of the current clinical trial design has been under scrutiny for a number of years with the sustainability of the exiting model under question. A critical success factor is adequate patient recruitment and retention. Recent initiatives to redesign the clinical trial process have focused on the creation of trials that are more patient focused. A wealth of medical grade physiological data is now readily available from wearable technology, with the potential to create a new future where patients no longer have to visit research sites and where real-time data are available remotely.

However, integrating wearables into a clinical trial is more complex than simply giving the patient a smartwatch and spontaneously generating clinically relevant data. Focusing on technology and sandwiching it into a trial is not a best practice. Wearables need to be viewed as a component of an overall patient-centric strategy rather than solutions in themselves. When creating a remote trial, simply shifting the burden from the sites to the patients, requiring them to carry out a number of tasks in an unsupported, uncontrolled environment is neither welcome nor sustainable. The process for successful selection and integration of wearables needs to take a number of criteria into consideration; clinical hypotheses, the

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value that is gained by the inclusion of wearables, the robustness of the data generated by the devices, and ensuring that the data adds clarity not additional complexity to the trial.

The re-engineering of the clinical trial to create a patient focused trial goes beyond mere convenience. Wearables and sensor have the potential to generate digital maps of individual's physical behaviours. Wearable technology is facilitating the remote capture of real life data but also has the potential to create new end points and outcome measures that are meaningful to the patient and could hold the key to a new clinical trials paradigm.

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Assessment and management of osteoporosis ——

SP0025 | **THE USE OF BIOMARKERS FOR OSTEOPOROSIS CLINICS**

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The balance between bone resorption and bone formation is maintained through a complex regulatory system of systemic and local factors acting on bone cells, such as calcium regulating and sex hormones, growth factors and cytokins. Furthermore, the competence of the bone cells and the number of active cells will determine the production of bone matrix proteins, while other incompletely understood intrinsic mechanisms will determine mineralization and micro-structure. Exposure of the matrix after osteoclastic activation allows for proteolytic enzymes to commence the degradation of the collagenous structure. The signals responsible for termination of bone resorption and initiation of bone formation (coupling) are not yet completely understood. Nevertheless, a tight coupling between resorption and formation is required to maintain bone mass and to preserve the micro-architectural integrity of bone.

Based on this knowledge markers of bone metabolism have been developed. These markers have been evaluated in terms of their ability to predict fracture, change in bone mass, and response to pharmacological treatments in clinical trials and additionally to monitor treatment in clinic.

The lecture will cover the use of markers in clinical trial, interpretation of change in markers from currently available and potential new drugs and to what extent and how to best apply in clinic.

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SP0026 | **NOVEL IMAGING TECHNIQUES FOR ASSESSING OSTEOPOROTIC FRACTURE RISK**

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The measurement of areal bone mineral density (aBMD) by dual x-ray absorptiometry (DXA) has been the mainstay for the diagnosis of osteoporosis for at least two decades. The sensitivity and specificity of this test, however, remains suboptimal. For example, more than 50% of postmenopausal women with fragility fracture are not identified with DXA. A great deal of research has been performed recently to develop alternative or complementary imaging techniques to overcome DXA predictive limitations. These techniques are based on the non invasive analysis of bone microarchitecture and estimation of bone strength by finite element analysis (FEA).

Texture analysis uses mathematical models based on fractal analysis to evaluate bone microarchitecture using various types of bone images. The trabecular bone score (TBS) has emerged as an approach that may improve fracture risk prediction. The TBS is based on the texture analysis of the DXA lumbar spine image to quantify bone microarchitecture. Several cohort studies have shown that a subset of individuals could be reclassified with TBS. A meta-analysis results have allowed for incorporation of the TBS in the FRAX score calculation, that is widely available.

The measurement of volumetric BMD with quantitative computerized tomography (QCT) at the hip has been shown to predict fracture risk. These images can also be used to perform FEA that may increase the fracture risk prediction. The additional value of this technique compared with DXA remains to be established in a clinical setting.

Bone microarchitecture can also be assessed at peripheral sites such as the distal radius and tibia using high resolution peripheral quantitative tomography (HRpQCT). Numerous cross-sectional and case-control studies have shown a significant association between prevalent fracture and bone microarchitecture and estimated bone strength assessed with FEA. The bone parameters measured at distal sites are also associated with fractures at distant sites, e.g., the vertebrae and the femoral neck. In a recent prospective study, bone microarchitecture at the distal radius - especially the trabecular vBMD - has been associated with incident osteoporotic fracture. The FEA models were also predictive of fragility fracture. The best models and the most appropriate architectural parameters - whether they are trabecular or cortical - remain to be dissected out and their comparative diagnostic value with aBMD by DXA remains to be established.

The measurement of the TBS may allow for reclassification of a subset of