Fibromyalgia Syndrome

A discussion document

FMS is characterized by widespread musculoskeletal pain, fatigue and cognitive difficulties. Central nervous system sensitization is a major component where various external stimuli eg infection, trauma and stress contribute to symptoms. The pain is neuropathic in nature, with changes in dermal unmyelinated nerve fibre bundles, while myelinated fibres are not affected.

The pain of FMS often has a burning, aching quality, and varies in severity and position. The pain is neuropathic in nature, with changes in dermal unmyelinated nerve fibre bundles, while myelinated fibres are not affected [(1)(2)(3).] Diagnosis is largely by exclusion of other diseases eg SLE, although the patterns seen with the typical trigger point tenderness and other symptoms usually makes the diagnosis fairly easy. The pain is not fixed, and it varies with a wide range of factors such as activity, age, drugs, hormonal action, diet, illness, season, stress and even weather change.

Environmental and genetic factors predispose individuals to develop fibromyalgia. Symptoms usually start after a precipitating event such as injury or acute stress, although in some it is a cumulative series of traumas or “activators” which can include physical trauma, especially MVAs with neck and shoulder injuries, stress, parasites such as blastocystis hominis, moulds, infections, or prolonged postural or rotational causes often occupational in origin. The onset of menopause may precipitate FMS symptoms, as this is a time of autonomic instability.

Recent research has made some significant progress in the probable mechanism of this neuroinflammation, both central and peripheral. FMS has been “linked to inflammatory reactions and changes in the systemic levels of pro-inflammatory cytokines that modulate responses in the sympathetic nervous system and hypo-pituitary-adrenal axis” [(7)]**.** Mendieta et al found higher levels of IL-6 and IL-8 than in healthy volunteers, and these 2 interleukins were 2 of the most constant inflammatory mediators in fibromyalgia, with levels corresponding to the severity of fibromyalgia symptoms, and that IL-6 and IL-8 could have additive effects in the continuous pain in fibromyalgia.

Inflammatory changes in glial cells in the brain has been reported, with the level of activation corresponding to the level of fatigue. Functional magnetic resonance (fMRI), demonstrate that activity is higher than normal in the areas of the brain that deal with pain, suggesting that pain signals are bombarding the brain or that the brain is abnormally processing pain signals from the body.

Increased levels of IL-6 and IL-8 in CSF and serum suggests symptoms are mediated by autonomic activity rather than the previously assumed prostaglandin associated mechanism, and these levels appear to correlate to the severity of the FMS symptoms. It is thought these have an additive effect in the continuous pain of FMS. The finding of increased levels of these in varicose veins lends another potential driver from the vascular compression syndromes.

Elevated levels of Substance P have been found in the CSF of FMS, probably a secondary rather than primary phenomenon. Substance P is a chemical released when a painful stimulus is detected by your nerve cells. More specifically, substance P is involved with the pain threshold, which is the point at which a sensation becomes painful. Elevated levels of substance P could help explain why the pain threshold may be lowered in people with fibromyalgia.

Pathogenesis

Backryd et al found “evidence of both neuroinflammation (as assessed in CSF) and chronic systemic inflammation (as assessed in plasma.) They also replicated previous research concerning increased levels of IL-8 in both CSF and plasma. They concluded that “fibromyalgia seems to be characterized by objective biochemical alterations, and the lingering characterization of its mechanisms as essentially idiopathic or even psychogenic should be seen as definitely outdated.” (4)

Small fibre neuropathy has also been documented in PTSD, Hashimotos disease, Complex Pain Syndrome, Sjogrens Syndrome, Lupus connective tissue disease, Sarcoidosis, Vitamin B12 deficiency, Coeliac disease, HIV, Amyloidosis, Paraproteinaemia, Alcohol abuse, Chemotherapy and Restless Legs Syndrome, suggesting a similar pathogenesis, notably diabetic (and pre-diabetic) neuropathy.

There is now increasing evidence that nerve compression can promote local as well as remote immune –mediated inflammation, resulting in activation of pain pathways nowhere near the area of compression. Patients with neuropathic pain from entrapment syndromes often present with symptoms outside the innervation area(5). Slowly progressive mild nerve compression can produce preferential degeneration of small nerve fibres, whereas myelinated axons remain largely intact. As a consequence, changes are not seen on standard Nerve Conduction Studies (6).

Many patients with FMS start with one or more trigger points described as myofascial points then progressively more are affected often at a time some distance from the original activating factor. Myofascial pain syndrome affecting localized areas is quite common, so that this and FMS are seen as simply variations of the same problem. With increasing hypersensitivity, driven by the “drivers” that differ in every person, scars, even freckles can be felt. Bodies become fatigued, yet unable to get to sleep with the activated fight or flight mechanism driven by catecholamines.

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Griffith University on the Gold Coast has established FMS to be part of the complexity of threat receptor hypersensitivity (see later on TLRs), and are working in an area called ion channellopathy. Other US researchers have found a very high incidence of non-myelinated small nerve fibre neuropathy (where there is significant damage to the small nerve endings especially in the skin) which explains the characteristic sensitivity to touch, and probably also explains the hypersensitivity in the vagus nerve which innervates the gut and heart producing symptoms of autonomic dysfunction (dysautonomia). Genetic researchers have made advances that help to explain why people confronted with the same activation processes may or may not develop POTS and fibromyalgia.

DNA in Fibromyalgia

DNA mutations thus found: (11) and Griffith University

- Ion channelopathy, (SCN9A, TRPV2, TRPV3): associated with development of FM and severity of symptoms
- DNA hypomethylation,
- Catecholaminergic – COMT mutations

- NO metabolism- associated with development of FMS and pain sensitivity (oxidative stress)
- Dopaminergic (DRD4)
- Serotonergic: anxiety-related traits, psychiatric symptoms, psychological distress

Overseas researchers have been mapping the DNA profiles in FMS. The ones I find most significant are the COMT (reduced capacity to metabolise catecholamines), MTHFR, IL-6, IL-8 (inflammatory cytokines) and eNOS and MnSOD/SOD2 (oxidative stress) mutations. The MTHFR mutation is so very common, and present in around 40% of the population, so it is no surprise that its long term problems are important in FMS.

Current research at Griffith University is exploring the array of Toll Receptor and Acetylcholine receptor polymorphisms that result in nerve hypersensitivity, altered channel ion channelling and cellular function that is involved in mast cell activation.

Turning off the Inflammation

Working through the problems leading to fibromyalgia, it is like opening Pandora's Box! But I have found that looking at the activators and drivers in these problems helps us take the next step forward towards recovery. The process is complex as so many processes are underway and all need to be sorted out.

Inflammation is at the basis of most disease. Inflammation, the immune response of body tissues to injury or infection, has been an important part of our innate immunity since we were cavemen. Acute inflammation is a normal process that protects and heals the body following physical injury or infection. However, if the agent causing the inflammation persists for a prolonged period of time, the inflammation becomes chronic, which can cause a wide range of problems.

Working out the things that are triggering the innate immune system Toll-Like Receptors (TLRs) is critical to dealing with these problems. But like Pandora’s Box, when you open this it can be very complicated with the multiple genetic factors, and various drivers we are only starting to work out. But each one you do can improve the quality of life in someone with this immeasurably. You may be aware of the increasing food intolerance you are experiencing, but removing physical drivers can slow this down so gradually these intolerances are less severe, or disappear.

When stress is less, with a reduced production of catecholamines, the stress or fight or flight chemicals from the adrenals, we can often eat the poorly tolerated foods, so sometimes it is hard to work out the culprits. Symptoms often disappear when stress is not present, so many people are considered to have only psychological problems, which is usually far from reality. I see anxiety and panic attacks increasingly as a simple catecholamine-driven reactions to mechanical or dietary triggering as well as psychological causes. So much anxiety is driven by mechanical causes, especially to the shoulder and spine, as well as foods the body sees as a threat.

Drivers

Drivers can be mechanical (as below), diet choice, stress again, hormonal fluctuation (especially at menopause when many FMS first become symptomatic), illness, moulds and other threats to the immune system and even weather change itself. I think of collagen like a guitar string. When the weather changes, you have to re-tune it. But as the inflammatory responses are being controlled, the activation reduces and you improve. People with hypermobility have increased responses associated with the “increased stretchiness” of their collagen.

The spinal drivers below are currently the subject of HRV studies to confirm activation, as seen in static preliminary testing. ANS innervation to different areas of the spine mean that symptoms vary depending on injury site. Thoracic and

upper lumbar spine are sympathetic, neck and low sacro-iliac are parasympathetic. TOS produces mixed results, although this is complicated in interpretation as the TOS may exert its autonomic activity through its mechanical effect on the brainstem

The spine is a major factor in triggering TLRs, especially in migraine and fibromyalgia. This is obvious in people following MVAs, whiplash and other spinal injury, but it also can be occupational, for example in hairdresser, dentists, nurses, who work with a rotated spine. There is likely to be an increase over future years as people become more dependent on their computers and tablets, while their posture is not attended to. This appears to be from local mechanical effects on the autonomic nervous system.

The concept of Central Sensitization, where pain and altered sensory states may be due to synaptic and membrane excitability changes in the central nervous system and not necessarily due to processes in tissues has been around for over 20 years, and this helps to explain a lot of things such as arthritic pain, where for example eating lectins [16] can produce typical arthritic pain in a hip or knee. Working out these food drivers, especially cow dairy, wheat, preservatives and lectins can provide remarkable reduction in pain (best seen in migratory/ variable arthritis.) I often find that after eg a shoulder or thoracic spine injury, pain starts in other areas, a knee, low back, neck etc, often followed by a cascade of seemingly unrelated problems including sleep disorder, “panic attacks,” IBS etc. Treatments are often directed to the back, knee, gut etc rather than the actual source of the problem.

The vascular compression syndromes, most prominently the thoracic outlet, popliteal, renal, and iliac vein compression syndromes are found in all POTS (Postural Orthostatic Compression Syndrome) patients in our studies (over 100 at this point) to varying degrees, and these are currently being investigated. Less common ones include Median Arcuate Syndromes. Details on these areas are covered very well in Prof Scholbach’s website:
http://wp12612379.server-he.de/wp-content/uploads/2015/12/Vascular-compression-syndromes.pdf

There are other compression areas- at the distal end of the adductor canal in the thigh, about 12 cm up from the end of the femur, particularly when seated, is one that is becoming increasingly apparent. Piriformis activation is very common, but so too is ilioinguinal, but it is difficult to establish if this is a primary problem associated for example with prolonged sitting, or secondary to flexion at T10/11/12 as has been documented by research physiotherapist Craig Phillips (DMA pilates Melbourne).

At this stage of the research, it is upper cervical and thoracic outlet compression that appears to be the most significant of the drivers established, although data has not yet been analysed. This combination is common after MVAs, where progressive dysfunction occurs, often affecting the gut, and appears to be a primary cause of the increasing anxiety and depression often seen, as well as the psychological impact of the fibromyalgia on their lives. Not surprisingly, as therapy to attend to the physical drivers proceeds, definite changes in psychological status has been found. Researchers have found that a lot of psychiatric disease is inflammatory, for example both schizophrenia and bipolar disease are driven by Interleukins 6 and 8. A formal assessment of anxiety and depression during treatment phases of the FMS drivers has been commenced here in 2019.

Activation

Disease activation appears to be by baroreceptor signalling, or local inflammatory responses to microemboli/microtrauma from the vein compression, or inflammatory chemicals eg IL-6, IL-8 and MCP-1 (monocyte chemotactic protein 1), found in sluggish blood (as seen in varicose veins,)[9] and possibly brainstem hypersensitization. But it is the alteration in the

autonomic nervous system response when compression is present that is probably the primary factor in most patients I see, and why our research is targeting the autonomic activation with the various areas of compression as well as the neck and spine where there is evidence of injury (often occupational or posture) or activated trigger areas.

With awareness of the various “drivers”, patients with fibromyalgia, dysautonomia, migraine and POTS are often able to differentiate the different “drivers” to these patterns of their problems, and from this comes realization of posture, and lifestyle change helps and this begins the path to recovery. For example, someone with popliteal compression may now recognize the paraesthesiae in their hands or feet with posture, and those with mid-thoracic spine injuries especially around T7 can recognize the tachycardia and wave of anxiety with rotation of the spine, followed by fatigue that may last for days.

Simply driving with arms outstretched can produce typical symptoms of a panic attack, and weight lifting can produce fatigue, headache and other symptoms. There is of course a blurring of boundaries, but generally as each driver is worked out, these can be nullified or modified by simple changes- most commonly with diet, posture, lifestyle, targeted pilates programs, and above all, knowledge of the underlying causes.

Looking at each of the contenders for pathogenesis.

1. **Vagal Activity and Baroreceptors**

“The vagus nerve (VN) is a key element of the autonomic nervous system and a fundamental component of the parasympathetic branch of the autonomic nervous system. This branch of the nervous system is not under conscious control and is largely responsible for the regulation of several body compartments at rest, overseeing a vast range of crucial functions, communicating motor and sensory impulses to every organ in your body. It is essential for regulation of the body’s immune response, and research is looking at the vagus in treatment of chronic diseases. (37)

Vagal activity results in various effects including heart rate reduction, vasodilation/constriction of vessels, glandular activity in the heart, lungs and digestive tract as well as control of gastrointestinal sensitivity, motility and inflammation. (37)

As a mixed nerve, the VN contributes to the bidirectional interactions between the brain and the gut, i.e., the brain-gut axis. In particular, after integration in the central autonomic network of peripheral sensations such as inflammation and pain via vagal and spinal afferents, an efferent response through modulation of preganglionic parasympathetic neurons of the dorsal motor nucleus of the vagus and/or preganglionic sympathetic neurons of the spinal cord is able to modulate gastrointestinal nociception, motility, and inflammation. (37)

Vagal tone specifically refers to the continual nature of baseline parasympathetic action that the vagus nerve exerts. While baseline vagal input is constant, the degree of stimulation it exerts is regulated by a balance of inputs from sympathetic and parasympathetic divisions of the autonomic nervous system, with parasympathetic activity generally being dominant. (38)

Vagal tone is frequently used to assess heart function, and is also useful in assessing emotional regulation and other processes that alter, or are altered by, changes in parasympathetic activity. Measurements of vagal tone rely mainly on heart rate and heart rate variability. Increased vagal tone (and thus vagal action) is generally associated with a diminished and more variable heart rate. However, during graduated orthostatic tilt, vagal tone withdrawal is an indirect indicator of cardiovascular fitness. (38)

The vagus helps keep anxiety and depression at bay, and opposes the body's reaction to stress. Over-compensation for a strong sympathetic nervous system response can cause syncope from a sudden drop in cardiac output, and can also lead to temporary loss of bladder control. An unexpected finding with the heart rate variability provocation studies has been the increased heart rate expected with adrenalin/nor-adrenalin but heart rate variability characteristic of parasympathetic activation, and the culprit, by and large looks to be the vagus and its web of plexuses.

The **baroreflex** or **baroreceptor reflex** is one of the body's homeostatic mechanisms that helps to maintain blood pressure at nearly constant levels.

Triggering of baroreceptors is thought to be an integral part of the autonomic hyperactivity found in POS. The mechanism for the abnormal function found in POTS is as yet unclear.

The **baroreflex** provides a rapid negative feedback loop in which an elevated blood pressure reflexively causes the heart rate to decrease and also causes blood pressure to decrease. Decreased blood pressure decreases baroreflex activation and causes heart rate to increase and to restore blood pressure levels. The baroreflex can begin to act in less than the duration of a cardiac cycle (fractions of a second) and thus baroreflex adjustments are key factors in dealing with postural hypotension, the tendency for blood pressure to decrease on standing due to gravity. (39)

The system relies on specialized neurons, known as baroreceptors chiefly in the aortic arch and carotid sinuses to monitor changes in blood pressure and relay them to the medulla oblongata. Baroreceptors are stretch receptors and respond to the pressure induced stretching of the blood vessel in which they are found.(39)

Baroreflex induced changes in blood pressure are mediated by both branches of the autonomic nervous system; the parasympathetic and sympathetic nerves. Baroreceptors are active even at normal blood pressures so that their activity informs the brain about both increases and decreases in blood pressure. (39)

The baroreceptors are stretch-sensitive mechanoreceptors. At low pressures, baroreceptors become inactive. When blood pressure rises, the carotid and aortic sinuses are distended further, resulting in increased stretch and, therefore, a greater degree of activation of the baroreceptors. At normal resting blood pressures, many baroreceptors are actively reporting blood pressure information and the baroreflex is actively modulating autonomic activity. Active baroreceptors fire action potentials ("spikes") more frequently. The greater the stretch the more rapidly baroreceptors fire action potentials. Many individual baroreceptors are inactive at normal resting pressures and only become activated when their stretch or pressure threshold is exceeded. (39)

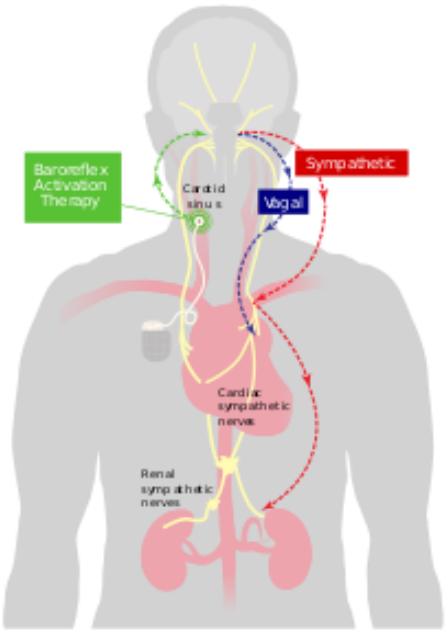
Baroreceptor action potentials are relayed to the solitary nucleus, which uses frequency as a measure of blood pressure. Increased activation of the solitary nucleus inhibits the vasomotor centre and stimulates the vagal nuclei. The end-result of baroreceptor activation is inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system. (39)

The sympathetic and parasympathetic branches of the autonomic nervous system have opposing effects on blood pressure. Sympathetic activation leads to an elevation of total peripheral resistance and cardiac output via increased contractility of the heart, heart rate and arterial vasoconstriction, which tends to increase blood pressure. Conversely, parasympathetic activation leads to decreased cardiac output via decrease in heart rate, resulting in a tendency to lower blood pressure. (39)

By coupling sympathetic inhibition and parasympathetic activation, the baroreflex maximizes blood pressure reduction. Sympathetic inhibition leads to a drop in peripheral resistance, while parasympathetic activation leads to a depressed

heart rate (reflex bradycardia) and contractility. The combined effects will dramatically decrease blood pressure. In a similar manner, sympathetic activation with parasympathetic inhibition allows the baroreflex to elevate blood pressure. (39)

The ability of baroreflex activation therapy to reduce sympathetic nerve activity suggests a potential in the treatment of chronic heart failure, because in this condition there is often intense sympathetic activation and patients with such sympathetic activation show a markedly increased risk of fatal arrhythmias and death. (39)



Source: Wikipedia. Baroreflex. https://en.wikipedia.org/wiki/Baroreflex: “Baroreflex activation is distinct from vagal stimulation. It works through an afferent limb which has the double effect of stimulating vagal output and attenuating global sympathetic outflow.” (39)

2. **Central Sensitization**

The concept of Central Sensitization, where pain and altered sensory states may be due to synaptic and membrane excitability changes in the central nervous system and not necessarily due to processes in tissues has been around for over 20 years.

Pain itself often modifies the way the central nervous system works, so that a patient actually becomes more sensitive and gets *more pain* with *less provocation*. It’s called “**central sensitization**” because it involves changes in the *central* nervous system (CNS) in particular — the brain and the spinal cord. Sensitized patients are not only more sensitive to things that should hurt, but sometimes to ordinary touch and pressure as well. Their pain also “echoes,” fading more slowly than in other people. This is also sometimes called “amplified pain.”

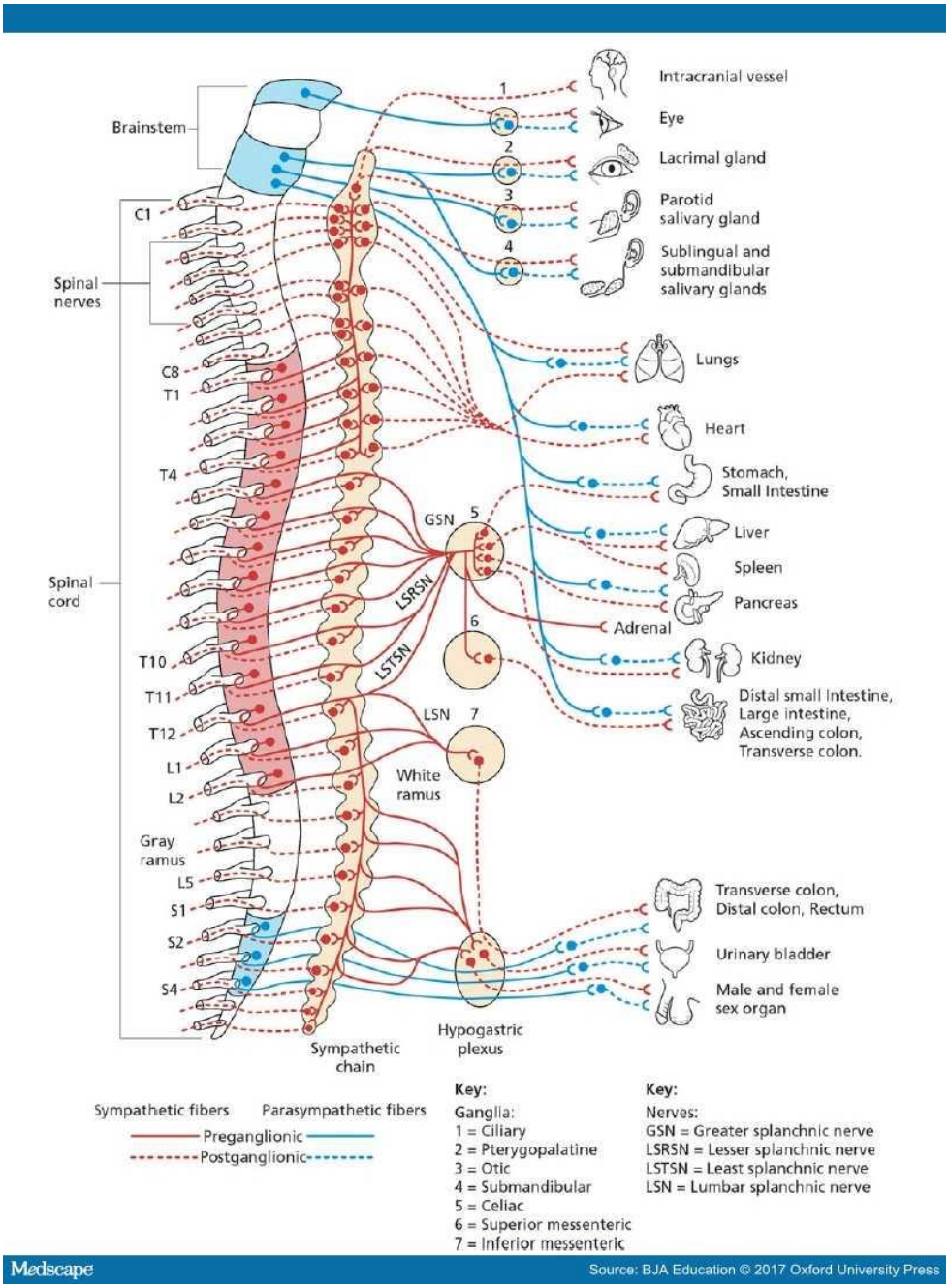
In more serious cases, the extreme over-sensitivity is obvious. But in mild cases — which are probably quite common — patients cannot really be sure that pain is actually worse than it “should” be, because there is nothing to compare it to except their own memories of pain.

3. **Sensitization of neural pathways**

Hypersensitivity following an injury is an important self-preservation mechanism, which allows the injured tissue to heal and to continuously warn / remind the brain to avoid further injury to this area. When this hypersensitivity becomes prolonged and develops into peripheral sensitization be it through either; increased sensitivity to the chemical modulators or a decreased threshold to the stimulus provides the body with no benefit. Peripheral sensitization is important to identify in patients as this can have an impact on treatment and their experience of pain as assessment through touch or movement may stimulate an unexpected level of pain. Peripheral sensitization manifests it's symptoms similarly to central sensitization. (35)

Some areas in the spine are seen to provoke similar symptoms of autonomic dysfunction- eg direct pressure on C1/2/3, where there is sensitization of cervical nerve root afferents and brainstem, (courtesy Dean Watson, https://watsonheadache.com/) injuries to the sacrum/coccyx from falls, and to the upper cervical spine, and appear to provoke parasympathetic responses as well as activating neural sensitization.

Sensitization occurs around T7 region in rotational activity (especially after seatbelt rotational injury or prolonged occupational activity), and sacrococcygeal joints (again usually a history of coccygeal injury,) although the autonomic response appears to be different to the thoracic spine injuries, with quite often marked adrenergic responses, consistent with the different sympathetic and parasympathetic pathways in these areas.



Source: Bankenahally, R., Krovvidi, H. Autonomic Nervous System: Anatomy, Physiology, and Relevance in Anaesthesia and Critical Care Medicine. BJA Education. 2016;16(11):381-387.

The sensitization appears to provoke autonomic symptoms with minor variations including posture. The responses can be quite dramatic and seemingly out of context with the activity. Craig Phillips from DMA Pilates Melbourne (https://www.clinicalpilates.com/) has provided evidence of the impact of rotational and other spinal injury on autonomic dysfunction, but also a pathway to recovery by addressing these mechanical injuries.

4. **Brainstem Connectivity in Chronic Fatigue Syndrome**

Dr Leighton Barnden, NCNED (National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, Griffith University, Southport), recently presented MRI data from NCNED at the 2019 Organization for Human Brain Mapping Conference titled "Connectivity within the brainstem is impaired in chronic fatigue syndrome".

“The brainstem, which consists of the midbrain, pons and medulla, has recently been implicated in ME/CFS. Three observations in cross- sectional MRI studies have implied that nerve signal conduction through the brainstem is impaired in ME/CFS. (33)

The researchers at Griffith University found that “ME/CFS is a common, debilitating, multisystem disorder of uncertain pathogenesis, for which there exists evidence of dysregulation of the central nervous system, immune system and cellular energy metabolism.” (33)

Leighton’s research reported significant differences were found between ME/CFS and healthy controls for connectivity within the brainstem. Impaired brainstem connectivity can explain reported autonomic and compensatory structural changes in CFS as previously reported by NCNED (Barnden, 2015, 2016), and may also explain the impaired cognitive performance, sleep quality and pain of ME/CFS.(33)

“Brainstem connectivity deficits were thought to be able to explain autonomic changes and diminish cortical coherence which can impair attention, memory, cognitive function, sleep quality and muscle tone, all symptoms of ME/CFS.” (33)

5. **Microembolic processes**

Compression of the popliteal and axillary/subclavian veins are known to produce emboli. In the extreme, sportspeople with TOS can get recurrent pulmonary emboli (Paget-Schroetters Syndrome.) Again, surgery to remove the first rib may remove the embolus risk but not the accompanying autonomic symptoms.

In recent research from USA looking at people seen at emergency departments after syncope or sudden collapse, 20% have been found to have had pulmonary emboli.(12) Dyspnoea in patients with known chronic obstructive pulmonary disease (COPD) can be a clinical challenge due to the nonspecific nature of atypical presentations. Typical features of fever, productive cough, and wheezing on presentation support COPD exacerbation, while absence of such findings may warrant further evaluation for underlying aetiologies, including pulmonary embolism (PE). It is suspected that one in four patients with atypical COPD exacerbation may have PE as an underlying or concomitant cause of acute dyspnoea. (16)

The lungs should filter out any microscopic emboli from the compression areas. I strongly suspect many of the people with “asthma” not confirmed on formal lung function testing, sometimes presenting at emergency departments with chest pain and shortness of breath, have had microscopic cascades. Sometimes there is a positive D-Dimer test suggesting a pulmonary embolus, but with no sign of DVT or embolus in VQ lung scans, the usual tests, they are discharged. In all patients where we consider this a possibility, we have started regular lung function testing, and if appropriate, HS-CT lungs.

Having an elevated homocysteine (>9) increases coagulability, just as it is known to increase CV risk, although the mechanism is not known, and because of this, not used by most clinicians. This provides a reasonable biomarker for the effect of the vascular effects from the MTHFR gene mutation. It may be that this association of increased homocysteine reflecting increased cardiovascular risk may be by increased microembolic risk, although increasingly it appears as though homocysteine simply reflects inflammatory load (similar to CRP which is itself driven by Interleukin-6, but CRP can be inaccurate in reduced complement C3, and autoimmune diseases such as SLE, so there one again is an overlap in problems).

The microembolic risk is so important to sort out in migraine, especially if there are hyperintensities seen on brain MRI (I believe mandatory in migraine with aura and cognitive impairment.) When a patent foramen ovale is present between the atria of the heart, microemboli from the vascular compression syndromes shunting through this into the brain may be responsible for cerebral damage particularly dementia, and certainly the "stroke-like" symptoms that affect some migraine sufferers.

In the brain MRI, migraine sufferers may have white spots, FLAIR hyperintensities. Often labelled as small vessel disease they can also reflect microembolic damage from the compression syndromes, but can also reflect "vasospasm" from the inflammatory chemicals (without a PFO.) Current unpublished research suggests 60% of severe migraine with aura have associated popliteal compression. We are currently reassessing the other vascular compression areas for this association.

Unfortunately the current level of radiology does not allow us the ability to differentiate between these hyperintensities, so you have to look for other clues. For example, retinal photography provides an answer to whether there is small vessel disease as in the retina, you actually see the vessels themselves.

6. **Catecholamine release (Takotsubo response)**

It is thought that baroreceptor signalling from the compression of the axillary structures trigger TLR (Toll-Like Receptor) activation which then activates an adrenal response which then produces catecholamines- a "Takotsubo response."

Case studies where observed cardiomyopathy occurs following trauma to a shoulder in 3 patients in the POTS cohort may implicate "Takotsubo response" as a major factor, (although microemboli potentially could cause the same response.) "Soft findings" of low sodium would suggest an effect on the adrenals. The increase in symptoms when patients are stressed would again suggest that it is the catecholamines thus released as a major factor. There are simply so many POTS patients with this process in place, but no "diagnosis," and I wish to coin the "Takotsubo Response" for these people. Case studies have confirmed that surges of acetylcholine can also produce the same symptoms.

POTS symptoms may persist in patients seemingly driven by VTOS following surgery to remove the first ribs, thus freeing the venous compression, but making the assumption that surgery can "fix" the problem is too simplistic. This then suggests that it is the scarring in the region or hypersensitization of the autonomics that produces the symptoms, as described by Christo in Practical Pain Management [(25)], and which would mean that the observed vein compression is only a guide to the presence of the compression producing the sensitization.

7. **Interleukins, TNF and other inflammatory chemicals**- .

"Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines are produced throughout the body by cells of diverse embryological origin. Cytokine is a general name; other names are defined based on their presumed function, cell of secretion, or target of action. For example, cytokines made by lymphocytes can also be referred to as lymphokines. Many of the lymphokines are also known as interleukins (ILs), since they are not only secreted by leukocytes but also able to affect the cellular responses of leucocytes. Those cytokines secreted by monocytes or macrophages are termed monokines. And chemokines are cytokines with chemotactic activities." [(32)]

"Interleukins (ILs) are a group of secreted proteins with diverse structures and functions. These proteins bind to receptors and are involved in the communication between leucocytes. They are intimately related with activation and suppression of

the immune system and cell division. Interleukins are synthesized mostly by CD_4^+ T lymphocytes, monocytes, macrophages and endothelial cells. There are 40 interleukins identified so far and some of them are further divided into subtypes eg IL-1α and IL-1β based on receptor chain similarities or functional properties." (32)

Elevated levels of pro-inflammatory cytokines are associated with many chronic diseases- cardiovascular disease, diabetes, auto-immune diseases, and even cancer. IL-6 (IL-8) and TNF release occurs in Takotsubo and is why the heart does not always return to normal after an "event."

These are also found in "sluggish blood" in varicose veins, so the reduced blood flow in vein compression may also contribute to the production of these, and as IL-6, IL-8 and TNF appear to be the primary factor in the multiple co-morbidities, especially fibromyalgia and Hashimotos Thyroiditis, they may contribute to the POTS comorbidities.

Increased IL-8 has been found in increased concentrations in the CSF in FMS, and IL6 and IL-8 are now thought to mediate the inflammatory response in FMS, and to have implications in the typical small fibre neuropathy that is the major part of the pain processing that is part of FMS.

Hypersensization in FMS is felt to be part of threat receptor hypersensitivity. There appears to be an array of TRP and Acetylcholine receptor polymorphisms that results in nerve hypersensitivity, altered calcium influx and cellular function - even immune responses.

Griffith University Gold Coast is exploring calcium channel (about 90 different ones) which then may influence monocytes differentiating into micro-glia to control brain blood flow. Glial cells are known as the "supporting cells" of the nervous system. The four main functions of glial cells are: to surround neurons and hold them in place, to supply nutrients and oxygen to neurons, to insulate one neuron from another, and to destroy and remove the carcasses of dead neurons.

The level of glial activation (inflammatory change) corresponds to the level of fatigue. Increased levels of IL-6 and IL-8 in CSF and serum suggests symptoms are mediated by autonomic activity.

Pro-inflammatory Cytokines:

- Interleukin-1 family: the major role of these is to act as a regulator of the inflammatory responses to tissue injury, as well as promotion of fever and sepsis. Two forms of the IL-1 family of cytokines, IL-1α and IL-1β, produced primarily in macrophages play key roles in autoimmune disease. IL-1 cytokines trigger IL-6, IL-8 and TNFα.

- IL-6 increases in response to infection, trauma or stress, and is associated with many autoimmune diseases and cancer. It is also found in diverticular disease, pancreatitis, diabetes and fatty liver. Body fat is the main source of IL-6. Interference in this pathway can cause unexpected obesity. It is the main trigger of CRP, a biomarker for the levels of inflammation in our bodies. It can be both pro-inflammatory and anti-inflammatory, and this appears to be dependent on markers such as waist circumference (although the boundaries are blurred as mutations here may result in increased waist circumference and obesity.) CRP is not always accurate and can be low in certain autoimmune diseases.

- IL-8 is produced early in the inflammatory response and controls activity of neutrophils, and persists for weeks once released. It is triggered by IL-1α, IL-1β and TNFα. Higher levels of IL-6 and IL-8 are found in the glial cells in fibromyalgia and these 2 are the most constant inflammatory mediators in fibromyalgia, with levels corresponding to the severity of fibromyalgia symptoms, and that IL-6 and IL-8 could have additive effects in the continuous pain

in fibromyalgia. Increased levels of IL-6 and IL-8 in CSF and serum in FMS suggests symptoms are mediated by autonomic activity rather than the previously assumed prostaglandin associated mechanism, and these levels appear to correlate to the severity of the FMS symptoms.

8. **Acetylcholine (Ach)**-

Part of parasympathetic activation- Griffith University has found acetylcholine to be associated with chronic fatigue by affecting ion channels in mitochondria, which produce the energy in our cells. Impaired mitochondrial exchange – with calcium signalling at an intracellular level could be a common denominator in fatigue-related diseases that have some autoimmune aetiology. Fatigue seems to be a constant even when genetic implications vary from one form of autoimmune disease to another.

Research from Professor Sonya Marshall-Gradisnik and her team at Griffith University on the role of Ach and dysfunction cell receptors in TRPM3 in chronic fatigue probably explains much of the fatigue that incapacitates many POTS patients. The transient receptor potential melastatin subfamily 3 (TRPM3) is one of the most primitive receptors in the body, activated by a wide variety of agents, from bacteria and viruses to temperature and environmental factors such as perfumes. This diversity made it a logical suspect for a condition like CFS that has so many different triggers in different people.

TRPM3 is an ion channel, controlling the way calcium ions are transmitted between cells and carrying instructions in the process. Calcium is a major signalling molecule in the cell so any impairment is potentially disruptive…although there are some compensatory mechanisms.

Increased acetylcholine responds best to slow graded exercise, as Drs treating fibromyalgia have found, and POTS becomes worse when patients are confined to bed, but experience has also shown the older concepts of pushing exercise even though it increases symptoms is counter-productive. Programs have to be specific for each patient and graded very slowly.

9. Dietary factors

Diet plays a major component in all inflammatory disease. There is increasing evidence that vascular disease, even hypertension, is inflammatory.

Recent studies confirm that the most important mechanisms in IBS include visceral sensitivity, abnormal gut motility and autonomous nervous system dysfunction. The interactions between these three mechanisms make bowel's function susceptible to many exogenous and endogenous factors like gastrointestinal flora, feeding and psychosocial factors. Recent data indicate that according to the above mechanisms, the influence of genetic factors and polymorphisms of human DNA in the development of IBS is equally important.[40]

“Most of IBS symptoms are directly related to specific abnormalities of ANS. The main characteristic of IBS patients is the increased activity of Sympathetic Nervous System (SNS) and the decreased activity of Parasympathetic Nervous System (PNS). There are differences between patients with diarrhoea and constipation as predominant symptoms and between men and women. [40]

It is believed that vagal dysfunction is associated with constipation as a predominant symptom whereas adrenergic sympathetic dysfunction is associated with diarrhoea as a predominant symptom. Other studies reported that IBS diarrhoea-predominant patients were shown to have cortisol hyper-responsiveness unlike that of constipation-

predominant IBS patients and controls. Other researchers observed elevated sympathetic dominance and vagal withdrawal during non-REM and REM sleep in diarrhoea-predominant IBS patients, but not in those with an alternating type of IBS. However, constipation-predominant IBS patients could not be distinguished from diarrhoea-predominant IBS patients or alternating type IBS with regard to autonomic nervous system. It is reported that there might be a continuum of autonomic dysfunction among these symptom-specific subgroups." (40)

The pathophysiology of irritable bowel syndrome (IBS) is complex and not fully understood, so Liu et al (42) studied whether visceral and somatic hypersensitivity, autonomic cardiovascular dysfunction, and low-grade inflammation of the gut wall are associated with diarrhoea-predominant IBS (D-IBS). They had a significantly higher systolic blood pressure and heart rate after a cold stimulus, indicative of autonomic cardiovascular dysfunction. They also had a significantly higher level of calprotectin. They also found significant correlations between visceral and somatic hypersensitivity, visceral hypersensitivity and autonomic cardiovascular dysfunction, and somatic hypersensitivity and autonomic cardiovascular dysfunction. (41)

The latest data indicate that the main mechanism inducing abdominal pain is the visceral hypersensitivity.(40) There is evidence that interactions within the brain and gut axis (BGA) that involves both, the afferent- ascending and the efferent-descending pathways as well as the somatosensory cortex, insula, amygdala, anterior cingulate cortex and hippocampus are deranged in IBS showing both the activation and inactivation. (43)

Alterations in the bi-directional signaling between the enteric nervous system and the central nervous system and consequently between the brain and the gut may play a significant role in the pathophysiology of IBS. (43)

The primary afferent neuron terminals of enteric nervous system (ENS) which are localized in submucosal tunica of gastrointestinal tract (Meissner plexus) and between smooth muscle fibres (Auerbach plexus) transmit stimuli to central nervous system (CNS) through sympathetic and parasympathetic autonomic nervous system (SNS and PNS). SNS transmits stimuli which are recognized as abdominal pain, whereas PNS transmits stimuli initiating a variety of reflexes. The pain stimuli through thalamus stimulate the cerebral cortex and permit the recognition of visceral pain. On the other hand, for the integration of visceral reflexes, the afferent stimuli through hypothalamus stimulate efferent neural fibres which through PNS stimulate or inhibit the contraction of smooth muscle fibres and the secretion of enterocytes in the gastrointestinal tract modifying the gut motility and secretion.

It is known that visceral sensitivity is regulated in many levels. Specifically this regulation is mediated at the level of enteric mucosa and submucosa, the level of spinal cord, the level of thalamus and the level of cerebral cortex. (40)

Low grade inflammation has been implicated as one of the underlying mechanisms of IBS. Variations in the circulating pro-inflammatory interleukin-6 (IL-6) levels and IL-6 gene polymorphisms have been demonstrated in IBS. Basasharti et al (45) found levels of pro-inflammatory interleukins 2,6 and 8 have been found to be elevated in IBS, especially in the post-infectious IBS (against non-post-infectious IBS) and reduction of anti-inflammatory IL-10 in both. (45).

Having variable or migratory arthritis- wherever, suggests a dietary cause. Having positive antibodies to the thyroid (Hashimotos thyroiditis) implicates an inflammatory and usually there are dietary components. The trick is to find the culprits here. Everyone is off doing gluten and dairy free diets, but most are wrong. It may be cow milk, as this is the first "toxic" chemical the body is exposed to in life, but after that there are many possible. Research in 1999 by Dr David Freed showed the deadly nightshades, the lectins, to be triggers to a wide range of autoimmune disease. But everyone has different triggers, and using the same diet in everyone simply does not work.

10. Impact of Stress

Chronic life event stress is a powerful predictor of symptom intensity in irritable bowel syndrome. The psychophysiological responses to such chronic stress should include alterations in cardiosympathetic and abdominal parasympathetic function. Autonomic dysregulation, consistent with the effects of chronic stress is a feature of IBS. Studies by Leach et al [(44)] on patients with constipation predominant constipation IBS demonstrated enhanced cardiosympathetic, and attenuated abdominal parasympathetic tone. IBS patients with predominant diarrhoea also exhibit enhanced cardiosympathetic tone but no apparent attenuation in abdominal parasympathetic tone. They felt that the predominant alteration of bowel habit may be associated with subtle differences in the overall pattern of central and abdominal autonomic reactivity. [(44)]

11. Mast cell Activation

"Mast cells play a key role in homeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury. An abundance of mast cells reside in connective tissue that borders with the external world (the skin as well as gastrointestinal, respiratory, and urogenital tracts.) Situated near nerve fibres, lymphatics, and blood vessels, as well as coupled with their ability to secrete potent mediators, mast cells can modulate the function of local and distant structures (eg other immune cell populations, fibroblasts, angiogenesis), and mast cell dysregulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders."[(10)]

The presentation of hives following a neck examination in a hypersensitive POTS/ fibromyalgia patient would implicate brainstem hypersensitivity as the underlying factor here. It is thought the mast cell activation is present in all POTS patients, swinging thought towards the neural sensitization theory of pathogenesis.

Discussion

The TLR Receptors (Toll-like receptors) are the threat response receptors that are activated by threats to the body, from baro-receptor activation, stress, trauma, inflammation, food we are intolerant of etc. The TLR receptors (of which there are 11 in humans) affect different areas, eg TLR 4 seems to be involved in pain pathways. The success of the TCA's, the old mainstay of medical treatment probably reflects their partial success is some people as they are effective in 2 of the human TLRs.

Changes in pain processes within the central nervous system lead to sensitization of pain pathways and its resultant clinical features, with lowering of pain threshold, and pain is often widespread. FMS is often reversible, but control of stress and other emotional factors are of critical importance. As mentioned, this is only part of dealing with the multiple triggers affecting the TLR receptors- these all need to be turned off to successfully treat FMS. The hypersensitivity makes pharmaceutical management very difficult as most sufferers are unable to tolerate medication at "normal" doses. There is often a hypersensitivity to chemicals, smells, sounds etc as well as barometric change.

FMS is common at all ages and in all societies, affecting females more than males. While most patients are middle-aged at presentation, it can be seen in children, teenagers and the elderly. Second only to osteoarthritis as the most common disorder seen by rheumatologists, it is recognised that FMS is an under-diagnosed and undertreated condition in general practice. FMS is poorly treated generally, I feel largely because of the constant pressure on time for over-worked GPs, and to a lesser extent in specialists who are probably more limited by the narrowness of their medical fields of expertise, but also a basic lack of knowledge especially while our educators lag behind in knowledge. FMS is a complex problem that requires a very detailed history to look at possible causes, and as consultations may take 90+ minutes, to include extensive family history to allow genetic modelling, it is likely to remain so.

FMS commonly occurs around the menopause when the autonomic nervous system is unstable. The symptoms of menopause especially the flushes and sweats are autonomic in nature, and reflect a dysfunction is autonomic stability; so controlling these is a vital part of FMS management. Menopausal dysautonomia may be the factor that tips someone with eg IBS and marital or work stress into full-blown FMS. It is not uncommon in children, although very difficult to diagnose accurately when they are very young. Fibromyalgia coexists with a number of chronic illnesses, ranging from inflammatory bowel disease and rheumatoid arthritis to osteoarthritis of the knee, and in this setting the clinical features of fibromyalgia will contribute to and often confuse the assessment of these disorders.

Turning off the threat receptors is vital to controlling the symptoms of FMS (SFN), whether it be physical or emotional stress, spine triggers, infections including the controversial dientamoeba and blastocystis and diet triggers which manifest as IBS. Simply using medication to control symptoms will not fix the problem. Taking narcotics to control the pain in reality increases the problem as morphine causes increased hypersensitivity to the already damaged nerves. Identification of young patients with localized symptoms is important to stop the progression to permanent damage.

Sleep disturbance has been identified as a major factor, and recent studies have reproduced FMS symptoms by inducing sleep deprivation in normal, although unfit subjects. EEG studies have shown a reduced amount of deep, non-dreaming, non-REM sleep with interruption by alpha waves. Increasing evidence shows that patients with FMS experience pain differently to the general population because of dysfunctional pain processing in the central nervous system. But the sleep disturbance is also characteristic of the heightened triggering of the threat receptors, the innate immune system activated and increased adrenalin output keeping the body on a “high alert” basis.

Food intolerance and its consequent problems appear to be present in almost all patients with FMS. Dealing with the intolerance is vital in controlling the fatigue and pain. In food intolerance, when you eat the relevant foods you are intolerant of, the innate immune system sees this as a threat and it produces a cytokine flux that affects the body in many potential ways including IBS, swallowing difficulties, fatigue, even bladder and potentially psychological effects. It is often difficult to work out which gut/ bladder symptom for example is driven by the autonomic activation or the food intolerance making the boundaries very blurred. Most people with food intolerances also have specific vitamin deficiencies associated with metabolic defects so these need to be sorted and treated, typical of the MTHFR mutation. These often include vitamin B12, vitamin D, Zinc, and Iodine. It seems to be at a metabolic level, but the mechanism is not yet understood.

Research from the allergist Dr David Freed implicates lectins as a major dietary factor.(16) This is particularly relevant if there is accompanying arthritis, especially rheumatoid arthritis, but the sensitivities can be to many different products. In others, it may be dairy, or wheat (or gluten), or sulphites among others.

I believe that the food industry is partly responsible for the increase in FMS, with heightened immune systems reacting to the tampering of our foods. Gluten is traditionally always the “fall-guy”, but in my experience, unless there is coeliac disease, it is our modified wheat, or cow milk products or sulphites, salicylates, amines that is more commonly at fault. You can take someone brought up on a dairy farm on fresh milk, move them to the city, change the milk and produce symptoms. You may be intolerant of wheat in Australia, but ok in Europe.

Scanning

Dynamic ultrasound demonstrates where some of the veins are compressed- axillary/subclavian, popliteal, iliac and renal. It is most likely that it is the triggering of the baroreceptors on these vessels that cause the problems, so even partial compression may cause symptoms. Thoracic outlet syndrome is increasingly being recognized clinically as a major cause of symptoms, but there are no scans at all available that will confirm or debunk the baroreceptor signalling theory. Only at present in clinical observation and heart rate variability can this be seen. But it remains uncertain if it is the impact on the vessels/tissues in the axillae, or the drive through the anterior scalene to pull on the C3 vertebra impacting on the brainstem.

Preliminary static heart rate variability studies have confirmed 3 distinctly different patterns of autonomic response, and through 2020 we will be looking closely at the different activation types as a response to mechanical changes in the body, eg straightening legs to provoke a response from the popliteal veins, as we do not know yet whether the damage from them is microembolic or associated autonomic change.

Management

But the theories become academic anyway. Management remains the same - work out the drivers, remove the ones we can, and control the immune response. I think people can be overwhelmed by the vast array of inflammatory things that are activated, and the biochemical changes that come with the underlying genetic stuff, and try to supplement their way out of it all. There are many practitioners struggling to get on top of these problems, but seem to “fix” on one source. I have no doubt I have not worked out all the processes, but the improvement in the patients looking in these directions provides at least a light for people in whom the future has appeared very grim.

Start with dealing with the obvious- the stress, the diet, obvious mechanical drivers which may be postural, and in TOS-driven symptoms avoid weight-lifting, working above the head, backpacks, heavy shoulder bags, prolonged computer work until scanning can determine the affected areas causing symptoms.

Where there is autonomic activation- sympathetic or parasympathetic, acupuncture provides an excellent starting point. Various types of acupuncture vary in effectiveness. At present we are using a Japanese style called “Kiiko” which directly targets the ANS. Good practitioners are able to pick whether a patient is in sympathetic or parasympathetic mode, and tailor treatment accordingly.

Exercise is paramount to good control of symptoms, and aerobic exercise such as walking has been unequivocally established as being vital to control of the FMS symptoms. It is known that exercise is possibly the only way to control acetylcholine. Many exercise programs are counter-productive, and each program has to be tailored to each patient.

It is with tertiary physiotherapy that long-term improvement usually starts to happen, although in some people just diet change may be sufficient to allow the body to deal with the other threats. There are a small number of physiotherapists adequately trained to identify and treat the mechanical and injured areas. This may lead to other exercise such as targeted pilates, yoga, Tai-Chi, and as the symptoms abate, exercise can be increased. Psychologists with specific knowledge of FMS are valuable in simply dealing with the psychological impact of the syndrome or in identifying repressed psychological trauma. There is a blurring of boundaries with PTSD, anxiety and depression with FMS and good management of these will reflect in better symptom control.

Medication

Duloxetine (Cymbalta) has provided valuable relief to many FMS patients, its relief thought to occur by lifting the nor-adrenaline in the nerve transmitters, thus controlling pain as well as accompanying anxiety and depression. But the benefit can be noted far earlier than expected when using this type of medication, so it seems likely that its success is through an as-yet unknown pathway, reducing neural sensitivity. Interestingly the generic version of this product simply is not as effective in pain control. Generics are not the same as the original products, which provides a possible area of research into exactly what is improving the pain, by looking closely at the 2 products.

Frequently (and traditionally) the tricyclic (TCA) antidepressants are used with limited success. It is thought that these products turn off 2 of the TLRs. Unfortunately Duloxetine is not easy for FMS patients to take because of their hypersensitivity to medication, and TCA's often cause tiredness. Morphine-like products should be avoided at all cost as these hypersensitize the already hypersensitive pathways, so a patient can end up dependent on drugs that really don't work and are only increasing the problem. Low dose Naltrexone and Medicinal Marijuana are used by a number of patients, but as yet I cannot comment on safety or effectiveness.

Conclusion

FMS can be controlled. It takes time and patience. There is no magic "fix" but a progressive dissection of the underlying problems will allow each to be dealt with. The addition of activated Vitamin B12 (or variant) may be needed in the MTHFR mutations, Turmeric and Magnesium usually very helpful. Working out diet triggers is vital, and listening to your body for the sources of activation, much of which is mechanical, and may be well away from the areas originally injured. High-level acupuncture is also a very useful tool, especially in controlling the inflammatory/ autonomic pathways. Cymbalta while hard to use, if tolerated, usually controls the neuropathic pain. Tertiary physiotherapy -(Connect, DMA, Watson) are 3 types I use dependent on individual mechanical drivers. When there are flares, you must identify what caused this. An almost universal driver is barometric change, and there is always an increase in patients with flare-ups when the weather changes. For most people, with patience, there is a pathway out of fibromyalgia.

Acknowledgments:

The author wishes to thank the invaluable assistance of QML Laboratories for providing access to multiple holter monitors, QScan Radiology, Absolute Ultrasound and Qld Xray for providing dedicated sonographers for various dynamic ultrasound scans, Dr Jonathan Marchand for insight into Thoracic Outlet Syndrome and mobile heart rate variability studies, Dr Geoff Adsett for provision of heart rate variability monitoring facilities, Dr Peter Jackson, of QScan Radiology for assistance in interpretation of MRI cerebral hyperintensities, Dr David Grosser, vascular surgeon for assistance with popliteal vein compression, Dr Ross Sharpe, cardiologist for many hours of guidance, particularly with the linking with migraine, Prof Pete Smith, immunologist, Dr Jon Jenkins, retired physician, Kelley Bright, dietician/exercise physiologist.

Special thanks to Mr David Haynes, acupuncturist who has combined to demonstrate using heart rate variability studies, the ability to reduce the autonomic instability with his "Kiiko" style acupuncture, and to Dr Christopher Soo for alerting me to the impact of thoracic rotation in my first recognized POTS patient.

Then the team of physiotherapists who have been assisting developing a program to treat the POTS patients- Tiele Santos and Indie Franke at Living Well Burleigh Heads who have made an invaluable inroads in TOS management, and to physiotherapists Stuart Stephenson (DMA Pilates), Melanie Roberts (Watson Therapy), Drew Singleton, Joe Roberts and Matt Roser at Core Physiotherapy, and to Liz Ciranni (Connect Therapy) and the ever- patient and enthusiastic Craig Phillips (DMA Pilates), who has provided 13 years of assistance looking at the mechanical forces at play in POTS, fibromyalgia, migraine and their co-morbidities.

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