Joining the Dots in POTS, Fibromyalgia and Migraine

One of the safest aspects about modern medicine is its conservatism, and the need to work within accepted and proven guidelines. It is a safeguard against enthusiastic or entrepreneurial management, and usually protects against unsafe and dangerous practices.

This discussion document does not follow mainstream evidence-based medicine and as such, it must be read and seen as research-based rather than evidence-based which is how medicine usually works, and which does provide a safety net against extreme concepts. More than anything else though, as the "dots" are joined, so too, disease processes and underlying mechanisms, start to become obvious.

Mainstream focus is usually limited to single "specialty" areas eg cardiology or neurology and these alone cannot hope to explain the complexity of POTS, fibro, autoimmune disease etc, and with links to cardiovascular disease, thyroid disease, diabetes, Parkinsons, and even emphysema and dilatation of the ascending aorta, another of our current research pro jects.
It is like opening Pandora's Box, and like a Russian doll, there is more and more inside.

The findings of autonomic instability as well as inflammatory responses caused by stress, mechanical and dietary factors has given us basis for working with problems such as neurological disease eg in footballers, currently attributed to brain injury as well as POTS etc. But it is far more complex than that, but the path is starting to become apparent, with diseases demonstrating varying levels of autonomic and inflammatory chaos. There is a plethora of research available but again, generally in specialty areas, and you have to read through each disease process to examine the inflammatory processes in each.

Working through the problems leading to POTS and fibromyalgia, my primary research areas, is like opening Pandora's Box- lots of things there! Essentially, we are all born with genetic predispositions to various things depending on our parents, and then it is what activates things- infections, parasites, injuries, other trauma etc etc that sets off the inflammatory pathways, and when this becomes chronic, mast cell activation chimes in with its own set of responses.

It has been looking closely at the disease patterns and finding the same inflammatory chemicals in all of them, whether it be a thyroid or a pancreas, or diverticular disease, aortic dilatation to name but a few. Then there is good data that IBS- associated inflammation produces the same inflammatory responses (namely ILs 2,6,8 and 10)[(1)] as has been seen to cause the neuropathic pain in fibromyalgia (IL-8),or ascending aorta dilatation and breast and prostate cancer (IL-6) you can see how dietary change alone can modify disease processes. In many women with autonomic instability, problems start with the menopause, and it is not surprising to discover that the flushes of menopause are associated with circulating IL-8 and TNFα. [(26)]

When I look at the patients in the research cohort, mechanical problems in areas especially the upper cervical spine and the thoracic outlet are very common- so when I look at any disease and its co-morbidities, I find a number of inflammatory chemicals- cytokines, interleukins and tissue necrosis at play along with autonomic instability- these have already been established, so the journey now is to work out how to deal with whatever "driver" is increasing the inflammatory responses, and modify their release.

Management remains the same most people – work out the drivers, remove the ones we can, and control the immune response. Some genetic factors can be influenced with dietary and other changes, most autonomic dysfunction can be significantly improved, and most

inflammation can be controlled to appoint were the body's own immune system is able to cope with the drivers. 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. We need to go to the grass roots.

Inflammation

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. Current disease research revolves around the TLR Receptors (Toll-like receptors) as being threat response receptors activated by threats to the body, whether this be trauma, food (or alteration in our food such as GM and preservatives) we are intolerant of, even stress etc- which provokes an immune response, causing the typical symptoms of IBS, chronic fatigue, migraine, dysautonomia, fibromyalgia, reflux oesophagitis to name but a few.

When stress is less, with less production of catecholamines, the stress or fight or flight chemicals from the adrenals we can often eat the trigger foods, or small quantities, 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 often far from reality. But stress itself activates the immune system with consequent cytokines response, and importantly the same ones as found in so many of the diseases we look at.

The spine is a major factor in triggering TLRs, especially in migraine and fibromyalgia. This is obvious in people following 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.

Recently researchers published data linking all types of auto-immune disease in children to the same threat receptors I mention above – so why not in adults? There is a lot of data emerging –slowly, but not linked, so when you put it all together patterns are emerging.

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. [(2)] 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. [(3)] 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.

The vascular compression syndromes, most prominently the thoracic outlet syndrome (TOS) are significant co-factors in the symptomatology in POTS (Postural Orthostatic Tachycardia Syndrome), and in POTS especially comes the complexity of what appears to be both sympathetic and parasympathetic activation, as well as inflammatory chemical release.

Other patterns are emerging. Many POTS patients describe symptoms starting after surgery, and various theories have attempted to explain this, but the most likely appears tom be from

hyperextension of the neck during the de-intubation. This was described by Andrew Holman in 2008 [22]. Similarly, non-epileptiform seizures have been identified with brainstem sensitivity driven through the C2 region of the cervical spine. The thoracic outlet compression does appear to affect this C2 region as well, making the pathways complex.

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.

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. Many people’s symptoms improve with simple attention to their posture and how they use their phones, computers, and even backpacks and bags they carry.

Specific case studies can demonstrate hives after a gentle neck examination, auto-immune activation from repetitive lifting when Thoracic Outlet Syndrome is present, and heart failure from repetitive lifting, although it is impossible at this point to ascertain if it is the brainstem from the C2/3 dysfunction or direct from the TOS.

Ongoing research in other areas especially Fibromyalgia, Migraine and Hashimotos Disease, has found the same vascular compression syndromes in the majority of patients, again suggesting disease activation by production of microemboli and/or inflammatory cascades which are released as the venous blood is released back into the circulation, (or perhaps simply from vessel walls when directly compressed) as well as any of the other inflammatory causes found in each patient.

But our research has shown that TOS compression appears to affect the scalene muscles to destabilize the neck at C2/3, or simply activate neural activation from compression around the scalenes and sternomastoid muscles affecting the C2/3 innervation where there is acetylcholine released as part of normal parasympathetic activation at that area as well as the brainstem sensitization. Or is it vagal stimulation? Researchers are now looking at “microtrauma” in the veins as a possible cause, and that concept is very appealing to me, with particular importance for unexplained chest pains (also from cascades of catecholamines and simple nerve compression at the axillae.

When other compression areas though are considered at the same time, it is vagal stimulation that appears to be the most likely source of the autonomic chaos. It all becomes very murky and complex, but does allow a path to recovery from the problems by addressing the mechanical issues, certainly until we have clear confirmation of the exact pathogenesis of the diseases.

Postural Orthostatic Tachycardia Syndrome (POTS)

“POTS is defined as orthostatic intolerance associated with tachycardia exceeding 120 beats per minute or an increase in the heart rate of 30 beats per minute from baseline within 10

minutes of changing the posture from a lying to standing position, in the absence of long-term chronic diseases and medications that affect the autonomic or vascular tone. There is no drop in blood pressure; it may even rise in the upright posture. Patients experience symptoms such as headache, nausea, tremors, sweating, palpitation and near syncope. Symptoms always occur in the upright posture and disappear on lying down."(7)

POTS was first described in 1933 by Dr Phillip Low at the Mayo Clinic, and it is considered one of the common conditions in young females. It occurs most commonly between the ages of 12 and 50 years with a male to female ratio of one:five. Patients with POTS are frequently labelled as having anxiety/neurosis or panic attacks."(7)

In many patients symptoms start abruptly following viral infections, trauma, surgery and after pregnancy. In some cases, there is a hyperadrenergic state leading to increased noradrenalin due to impaired clearance or decreased uptake of noradrenalin by the synaptic cleft. These patients suffer from profuse sweating, anxiety, tremulousness, tachycardia and high blood pressure. Lack of understanding of POTS has meant that many patients with this condition are frequently labelled as having anxiety/neurosis or panic attacks. (1) This variety usually runs in families.

The literature describes that there is a secondary form of the disorder seen in conditions associated with autonomic neuropathy, e.g. diabetes mellitus or amyloidosis, and in conditions that may be associated with intrinsic abnormalities in capacitance vessels, e.g. hypermobility syndromes. In other conditions the underlying pathogenesis is less clear, e.g. Sjögren's syndrome."(8)

The current research here challenges the current concept of the secondary form, and patterns are emerging, that both confirms the importance of hypermobility, but that it is generally vagal dysfunction that is the driver in perhaps all POTS, and the diseases with autonomic neuropathy secondary to the inflammatory responses derived from the emerging POTS "activators and drivers." POTS has co-morbidities that include fibromyalgia, migraine, auto-immune disease especially Hashimotos Thyroiditis, IBS, chronic fatigue and dysautonomia. Increasingly it becomes possible to see POTS and its co-morbidities as all part of the same process.

In our study of over 100 consecutive patients with established POTS, all were shown to have one or more venous compression syndromes. The overwhelming majority had venous Thoracic Outlet Syndrome (VTOS) usually coupled with neurological symptoms (NTOS) but normal standard testing with nerve conduction testing. Other compression areas included renal vein compression, often with ovarian vein reflux (Nutcracker Syndrome), iliac vein compression (May-Thurner Syndrome) and Median Arcuate Syndrome. Most had varying levels of popliteal vein, adductor canal and femoral vein compression.

It is challenging to the clinician to comprehend the impact of these areas of compression, when it is not even known what is "normal," where there are limited population studies, and the mechanism of how this compression affects the autonomic and inflammatory chaos of POTS is still unclear.

It is in this area where venous (and neurological) compression is occurring and is driving the POTS symptoms that the current research is working, to unravel the underlying mechanisms. It is the mechanism by which compression affects the autonomic stability that has proven difficult, but the pathway is now largely clear as the thing that binds these is the vagal complexes that envelop these regions. Following or part of these processes comes the co-

morbidities especially fibromyalgia, migraine, and auto-immune disease. The long process of data collection and interpretation has started to confirm and interpret these findings.

When I look at the patients in the research cohort, mechanical problems in areas especially the upper cervical spine and the thoracic outlet are very common- so when I look at any disease and its co-morbidities, I find a number of inflammatory chemicals- cytokines, interleukins and tissue necrosis factor at play along with autonomic instability- these responses have already been established, so the journey now is to work out how to deal with whatever “driver” is increasing the inflammatory responses, and modify their release.

Activation of POTS

Close examination of patient histories and examination provides a positive direction for clinicians and the people with POTS, and this approach is equally as effective in migraine, fibromyalgia and the other co-morbidities. Constantly asking the simple question “Why or how could that cause those symptoms?” and looking very closely at the history of the origin of the symptoms usually provides most of the answers, to what drives the symptoms, and with this a direction in management, without focusing on the currently largely untreatable (at the present time) DNA mutations and other areas of research. It enables clinicians to look at lifestyle, mechanical problems, and external inflammatory sources rather than being restricted to medication or supplements.

Most POTS patients have clear points of activation, eg trauma to neck or coccyx or shoulder. It may be cumulative until something tips them over the edge into a dysautonomic state. Common presentations may be mild symptoms associated with an occupation where overhead lifting is predominant, then a period of increased lifting, or stress, or virus etc may cause immediate activation. Once activated, the “drivers “ may be varied, requiring close attention to history, family history (DNA if available), diet, work and social practices, then looking for areas where autonomic and inflammatory activation is occurring. Only then can the process of recovery start in POTS.

As mentioned previously, ongoing research in POTS and other areas especially Fibromyalgia, Migraine and Hashimotos Disease, has found the same vascular compression syndromes in the majority of patients. These compression areas, particularly the thoracic outlet syndrome are so very important in almost all the dysautonomia I come across, but only the thoracic outlet, seemingly the most common, is described below (with more detail in a separate article), the others in “Intra-abdominal Compression Syndromes and Popliteal Vein Compression.”

Thoracic outlet syndrome

Thoracic outlet syndrome (TOS) is not the name of a single entity, but rather a collective title that encompasses a variety of conditions produced by compression of nerves, arteries and or veins (or all) because of an inadequate passageway through an area (thoracic outlet) between the base of the neck and the armpit. The thoracic outlet is bordered by the scalene muscles, first rib, and clavicle. This is described in this article as it has subjectively appeared to be the most common “driver” in dysautonomia in POTS.

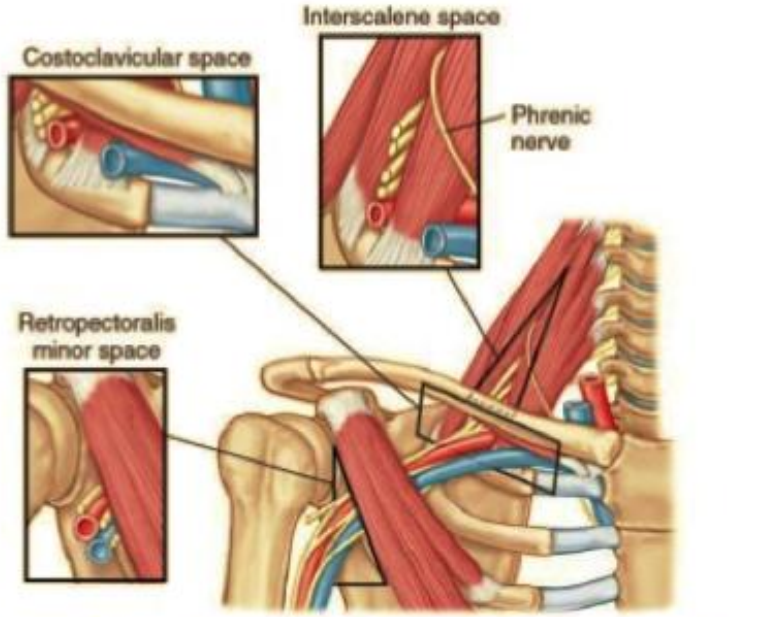


FIGURE 59-2 Three spaces in the thoracic outlet that may be responsible for thoracic outlet syndrome.

Source: https://www.slideshare.net/swatcats2013/thoracic-outlet-syndrome-62735055 (10)

Shoulder disorders, which include unspecific shoulder pain and specific disorders, are commonly diagnosed in primary care and often lead to prolonged disability. Their 12-month prevalence in the population of working age range between 7 to 47% for shoulder pain, depending on the population studied. The impacts for workers are important in industry such as in office, especially for chronic shoulder pain. (20)

"Although neck and arm pain is a frequent presenting complaint in the general population, the controversial and difficult to diagnose Thoracic Outlet Syndrome should always be considered especially if the risk factors and occupational situations associated with it as assessed. The neurogenic forms are by far the most frequent as they represent more than 95% of all cases of TOS, and these can be classified in the "true" neurological form associated with neurological deficits (mostly muscular atrophy), and painful neurological forms (with no objective neurological deficit). These painful forms are very frequent, especially when patients are systematically screened for these symptoms. The existence of these forms of TOS remains controversial in part because muscular and neurological manifestations are strongly interrelated. (20)"

"Nearly all cases of TOS (95%) are neurogenic in origin. NTOS is an underappreciated and often overlooked cause of shoulder and neck pain and numbness. Like patients with other chronic pain conditions, patients with untreated neurogenic TOS experience a diminished quality of life, reduced financial well-being, functional limitations, and an increased risk for depression and anxiety.(21)"

"Although the notion of NTOS as a complex spectrum disorder provokes some controversy in the field, its impact on patients is beyond dispute. Data indicate that the quality of life for a patient with untreated TOS is as impaired as that of someone with chronic heart failure. (21)"

"Neurogenic TOS occurs in an estimated 3 to 80 per 1,000 individuals, the wide range reflecting the lack of confirmation in many patients with signs and symptoms indicative of the condition. Women with NTOS outnumber men by 3 to 4:1. The

syndrome is particularly common in people who perform repetitive tasks with their upper extremities, such as violinists, data entry personnel, and workers on assembly lines. Athletes with repetitive overhead arm motion, including volleyball players, swimmers, baseball pitchers, and weightlifters, also are at increased risk, as are people who have experienced neck trauma. (21)"

Any condition that results in enlargement or movement of these tissues of or near the thoracic outlet can cause the thoracic outlet syndrome. Other risk factors include shoulder trauma, occupations or sports that involve heavy usage of the upper extremities against resistance, including jack-hammer operators and dental hygienists, weight lifting, pregnancy, poor posture and obesity. Rarely lung and mediastinal tumours can affect the outlet.

"Histologic studies suggest that injury to either the anterior scalene muscle (ASM) or the middle scalene muscle are the main causative factors of NTOS. Muscle fibrosis is a prime finding on examination of excised scalene muscles, with NTOS patients having 3 times as much scar tissue as unaffected subjects. The ASM derives from the transverse processes of the C3-C6 vertebrae. The muscle, which attaches to the first rib, serves as an accessory muscle of respiration, and also rotates the neck slightly. Spasm of the ASM puts traction on the brachial plexus and causes oedema of the muscle and nerves, which, in turn, limits the space of the outlet. Development of scar tissue and fibrosis of the ASM further worsen neural compromise and perpetuate pain. (21)"

Thoracic outlet syndrome symptoms include neck, shoulder pain, arm pain, numbness and paraesthesiae (pins and needles) fingers and impaired circulation of the extremities (so there may be for example, discolouration of the hands.) Symptoms can be constant or intermittent depending on what activities are being performed.

"It has been reported that the 3 most disturbing preoperative symptoms are pain at rest (87% of cases), feeling of numbness (66% of cases) and decreased strength (55% of cases). In practice, the patient often reports vague, poorly defined, and inconsistent symptoms, but clinical interview often reveals difficulties during activities requiring elevation of the arms (hanging up the washing, brushing one's hair, etc.).(20)"

Thoracic outlet syndrome was first described in soldiers with loaded backpacks who developed pain, numbness and arm fatigueability as they stood at attention, and results published in 1943.(19) "The mechanism of compression involved downward movement of the clavicle against the first rib, with a resultant tendency to shearing of the neurovascular bundle." (23)

This same mechanism was thought to explain subclavian vein thrombosis precipitated by prolonged heavy exercise of the upper extremities- Paget-Schroetter Syndrome. De Silva then described the same mechanism occurring in heavy breasted women with tight bra straps again shearing the neurovascular bundle.

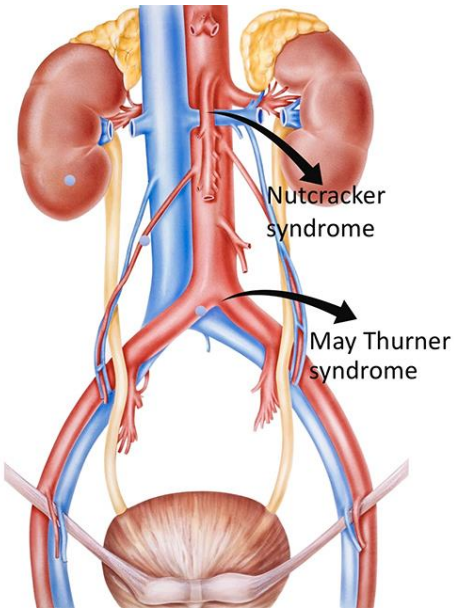
Thoracic outlet syndrome has been recognized for decades, but only since we started looking at the inflammatory response in popliteal compression in migraine has this area become more important. Illig and Doyle (23) write: "the subclavian vein is highly vulnerable to injury as it passes by the junction of the first rib and clavicle in the anterior-most part of the thoracic outlet. In addition to extrinsic compression, repetitive forces in this area frequently lead to fixed intrinsic damage and extrinsic scar tissue formation. Venous thoracic outlet syndrome progressing to the point of axillosubclavian vein thrombosis, variously referred to as Paget-Schroetter syndrome or effort thrombosis, is a classic example of an entity which if treated correctly has minimal long-term sequelae but if ignored is associated with significant long-term morbidity."

Other Compression Syndromes

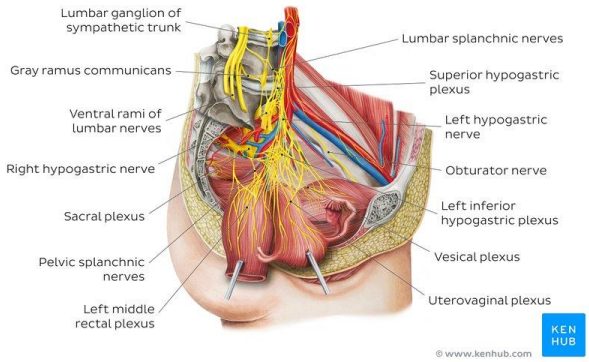
Venous thoracic outlet compression has been associated with intractable migraine. From ongoing research underway at present there is an between popliteal vein compression syndrome and migraine- this is most likely from cascades of inflammatory responses (and /or micremboli) that form when the blood is stagnant when the popliteal, axillary or subclavian veins are compressed, or microtrauma to the vessels, or once again autonomic activation.

I feel Pelvic Congestion Syndrome fits into the same category as the popliteal and thoracic compression but this is beyond the scope of this article, while management options are being established, and patients are being assessed for this. Irrespective of the initial cause, ongoing symptoms appeared to be driven by identifiable drivers, especially the spine, food intolerance, posture and arm and leg positioning in the vascular compression syndromes.

Commonly I find renal vein compression, where the renal vein jams under the Superior Mesenteric Artery. Sometimes it creates ovarian vein dilatation and retrograde flow (Pelvic Congestion Syndrome) It is not enough to excite the vascular surgeons (see Nutcracker Syndrome) for increasingly it is the coeliac plexus that envelops this area that is the most likely culprit where this is the primary driver. There is also iliac vein compression periodically noted. It is likely the mechanism is the same when the nerves of the pelvis are examined for compression areas.

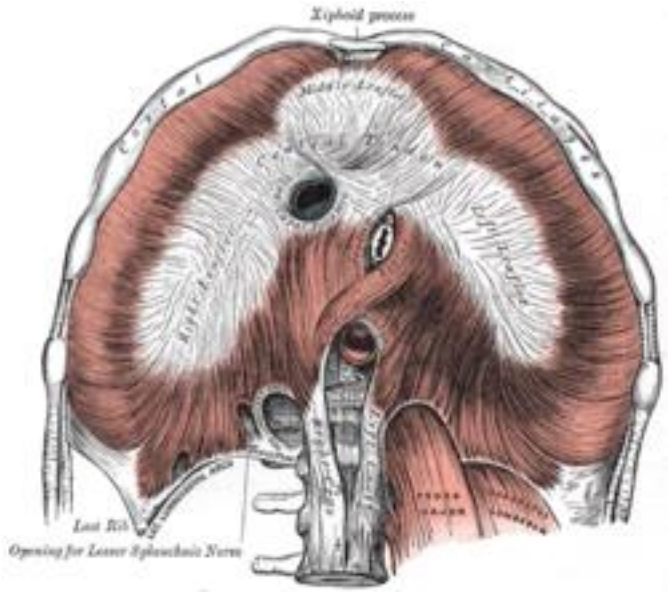


Source: Dr Kurian Mylankal
http://www.vascularcareadelaide.com.au/vein-compression.html



Source: https://www.kenhub.com/en/library/anatomy/neurovascular-supply-of-the-pelvis

I have been seeing an increasing number of Median Arcuate Syndromes where the coeliac plexus is being jammed by the median arcuate ligament at the bottom of the diaphragm compressing, or pinching the coeliac plexus nerves over the coeliac artery.



Source: Wikipedia: Gray's anatomy

These are mechanical problems, the popliteal compression generally easily overcome with postural change while the thoracic compression was more insidious, often with very subtle if any symptoms at all. In many, awareness was all that was required to manage symptoms, while others are being managed by physiotherapy programs that are being developed by the management team.

DNA in POTS

DNA is so very important. The mechanical and other activators and drivers do not cause symptoms necessarily in other people, and it appears to be DNA polymorphisms that provide the difference.

- hEDS and hypermobility causing increased signalling from "increased stretchiness."

- Methylation mutations (especially MTHFR) usually (100% in migraine), the 677 MTHFR mutation typically is associated with increased homocysteine, and probably affects collagen function as well as increased thrombotic risk.
- COMT frequently (= reduced ability to process catecholamines)
- Oxidative stress eNOS, SOD2. NO metabolism- associated with the development of FMS and pain sensitization
- IL mutations
- TRP mutations(threat receptors)- TRPM3 appears critical in NK immune cell function. TRPA1 is a key ion channel that detects oxidative stress and a range of endogenous and exogenous chemicals (smoke, solvents, cold air)
- Acetylcholine receptors (acetylcholine affects mitochondria causing fatigue).

Fibromyalgia

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.

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" [(21)]**.** 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 sympathetic 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.

Small fibre neuropathy has also been documented in PTSD, Hashimotos disease, Complex Pain Syndrome, and Restless Legs Syndrome, suggesting a similar pathogenesis.

DNA in Fibromyalgia

DNA mutations thus found:

- 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)
- Serotinergic: 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.

Migraine

Migraine is about inflammation. Genetic information points to the involvement of transient receptor potential (TRP) channels in pain mechanism. TRPA1, an ion channel on the trigeminal (and most other sensory) nerves is the major oxidative threat sensor. It is activated by various irritants and agents releasing the pro-migraine peptide, calcitonin gene-related peptide through this nerve pathway. TRPA1 agonists release chemicals that cause vascular dilation.

Most migraine appears to be driven by cervical nerve root sensitivity. The cervical afferents of C1-3 are the reason we get increased sensitisation of the brainstem. The common pathway with the Trigeminal nerve will present as the head pain or facial pain plus associated symptoms of dizziness and nausea etc (C2/3). The head pain is a representation of the input from the cervical afferent nerves C1-3. This constant input will reduce the latency period (ie someone will get symptoms earlier than the normal person).

This constant input then causes the brainstem to become sensitised and effectively “ready to go” with small input. This is why small variations (small C2 rotation perhaps from bad posture) or triggers will bring on large changes so quickly. The changes of this C2 rotation can very subtle and hard to find unless therapists are experienced in assessing these. (courtesy https://watsonheadache.com/

Successful management of migraine is really about “turning off” the processes that are driving the inflammation. In most people I see they are driven by the neck, sometimes thoracic outlet, although frequently it is very difficult to separate the TOS and C2 drivers, something that is part of our current research.

Certain foods that are “vasoactive” such as red wine, chocolate and aged cheese are well-known triggers. In women, hormonal changes at the times of menstruation can be a trigger. Sometimes it can be weather changes, or glare while driving, and the triggers can be obvious, but sometimes they can be very difficult to determine.

To complicate this is the research that implicates PFOs (Patent Foramen Ovale) as a cause of migraine “auras” in a number of adults (and it may be it is the same for kids), and again PFOs cause an inflammatory response, and when there is an aura (as described below) we may be looking at emboli (little TIAs or strokes) . There are not restricted to the brain as other vessels can be affected. The biggest problem I can see is the potential for dementia if this is not identified if present. Once the brain is damaged, it cannot repair itself. **It does not mean though, that if you have auras you have a PFO and will get dementia. At present, the current thinking is that they are both common, and that a percentage of people with migraine who also have PFOs, which puts them in the risk for vascular disease, and should be assessed correctly.** At present, as the knowledge is expanding we must review these periodically to see where the understanding of the condition has progressed and whether changed are required in management. We also believe now, that if we can eliminate the migraines, especially the auras, we probably need to do no further investigation at present.

The link between migraine and PFO was identified some years ago. Getting accurate trials has been very difficult to achieve, but when the patient selection criteria are correct, we are able to provide an 85% cure rate from migraine with the closure of the PFO. The other inflammatory processes discussed above also need to be addressed.

Around 20 to 25% of the population in general have foramen ovales that do not close at birth, but only a small percentage of patients with a PFO suffer with migraine and certainly not all migraine sufferers have a PFO. PFO is more common in migraine patients than in the general population- approximately 40 to 60% of people with migraine with auras have PFOs.

Approximately 40% of all strokes have no obvious cause, and this is more common in the under 60’s. In this group there is a higher percentage of PFO. The risk is higher if there is any medical condition that raises the pressure in the right side of the heart eg lung disease, pulmonary hypertension, pulmonary embolus, Obstructive Sleep Apnoea, DVT, cancer or any severe acute or chronic illness. The presence of an atrial septal aneurysm (mobile atrial septum) associated with a PFO or atrial septal defect also increases the risk of TIA/ stroke to 5% yearly.

Those who should be referred for assessment for a PFO include:

1. The severe migraine with aura non responsive or intolerant to usual therapy.
2. Blindness, hemiplegia or other significant neurological events would be a strong indicator for assessment (especially those whose employment is at risk or these events would place them or others in physical danger ie commercial pilots and divers).
3. Anyone who we feel may have had a TIA (mini-stroke). Generally neurological symptoms lasting more than 20 mins in a migraine event could be TIA
4. Migraine or anyone with unexplained changes in the brain MRI (or CT Spect)
5. Migraine with aura who feel they have cognitive decline
6. Severe migraine variants eg vestibular, abdominal
7. The other masquerader is multiple sclerosis. If it’s obviously MS so be it but some just don’t behave clinically like it and the follow up MRIs don’t fit
8. PFOs cannot be reliably diagnosed on an echocardiogram, the test most doctors use. They may need a Transcranial Doppler The actual PFOs are often very small, and may be only the size of a pinhead so there are no functional problems occurring in the heart.

<u>Looking at each of the contenders for pathogenesis.</u>

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. (28)

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. (28)

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. (28)

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. (29)

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. (29)

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. (30)

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.(30)

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. (30)

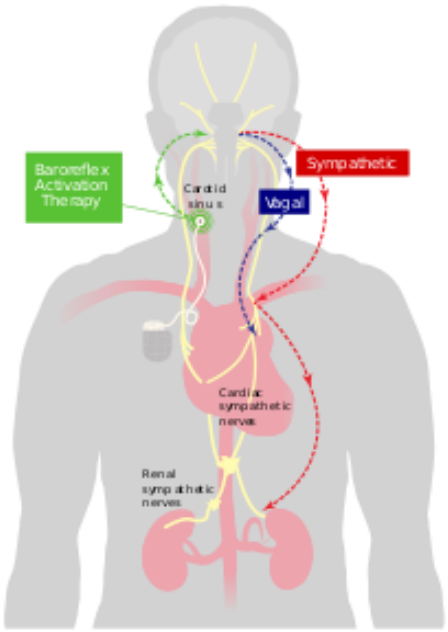
The baroreceptors are stretch-sensitive mechanoreceptors. At low pressures, baroreceptors become inactive. When blood pressure rises, the carotid and aortic sinuses are distended further, resulting in increased stretch and, therefore, a greater degree of activation of the baroreceptors. At normal resting 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. (30)

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. (30)

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. (30)

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. (30)

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. (30)



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.” (30)

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.”

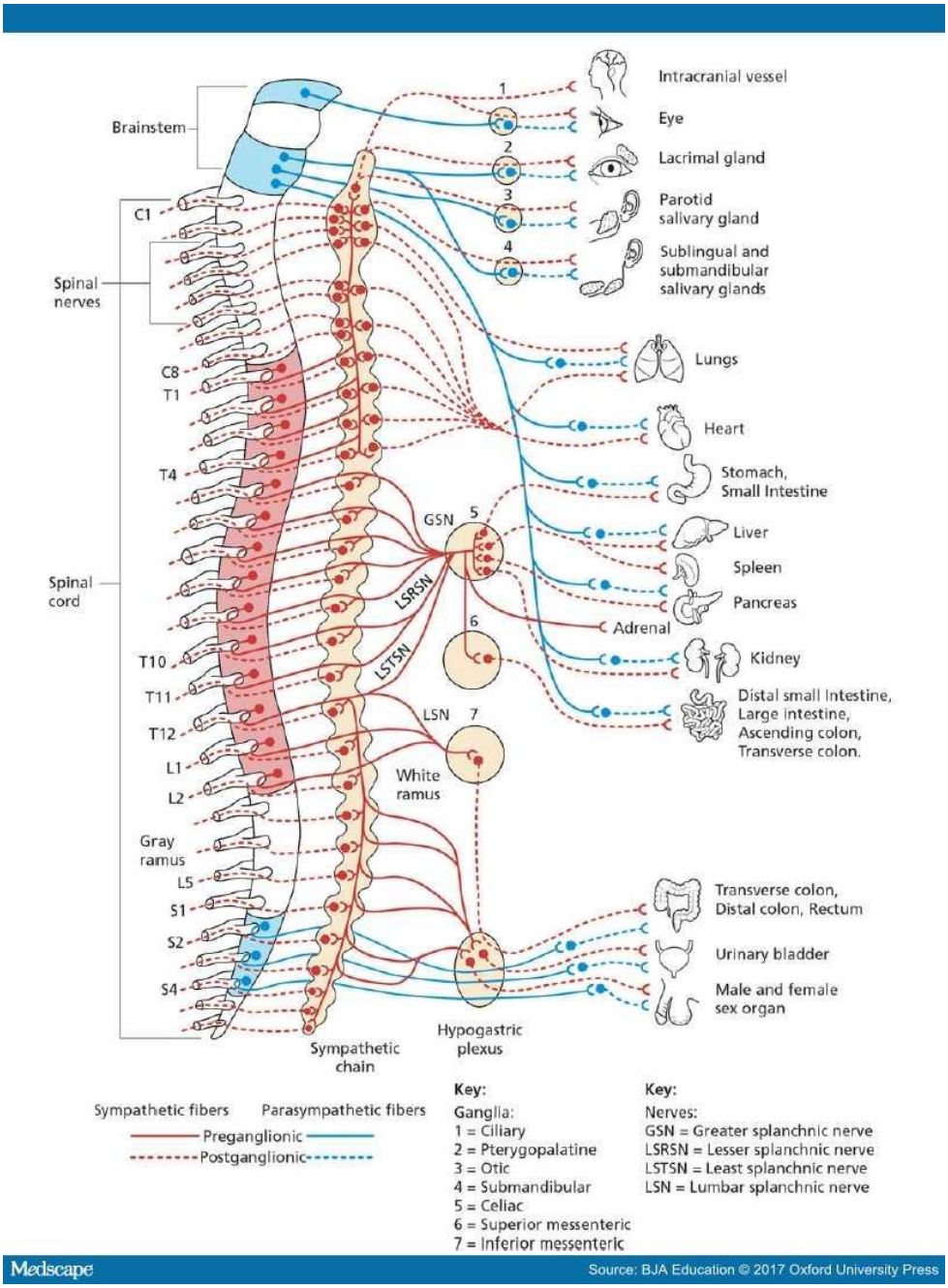
In more serious cases, the extreme over-sensitivity is obvious. But in mild cases — which are probably quite common — patients cannot really be sure that pain is actually worse than it “should” be, because there is nothing to compare it to except their own memories of pain.

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. (26)

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. (24)

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.” (24)

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.(24)

“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.” (24)

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.” [22]

“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.” [23]

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.(31)

“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. (31)

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.” (31)

The pathophysiology of irritable bowel syndrome (IBS) is complex and not fully understood, so Liu et al (33) 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. (32)

The latest data indicate that the main mechanism inducing abdominal pain is the visceral hypersensitivity.(31) 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. (34)

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. (34)

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 fibers (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 fibers which through PNS stimulate or inhibit the contraction of smooth muscle fibers 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. (31)

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 (36) 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. (36).

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 **(35)**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. **(35)**

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."(4)

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

Driver fatigue and even panic attacks driving is very common in POTS. The activation appears to be through thoracic outlet compression, but increasingly I am seeing what I believe to be Adductor canal compression and ilioinguinal entrapment syndrome. Both of these should be easily managed with attention to seat position and driving position.

The spine is a major factor in triggering TLRs, especially in migraine and fibromyalgia. This is obvious in people following 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. Orthopaedic research firmly targets the increasing use of mobile phones and computers for prolonged periods in the activation of these problems.

Shoulder pain is just so common, often not improved and even worse with our normal shoulder treatments, but retracing the injuries there is often a thread implicating an injury to the thoracic outlet rather than the shoulder itself, and as the rotator cuff wears anyway, this ends up as a diagnosis as scans show worn rotator cuffs, so the real problem is missed, and it becomes a treatment failure. An easy clue to thoracic outlet syndrome is the frozen shoulder.

The overwhelming evidence from the POTS study showed the presence of one or more vascular compression syndromes in all patients. Pelvic Congestion Syndrome is highly likely to be associated with this, and I expect we will ultimately find this to be every bit as important, (possibly more so depending on severity,) as the popliteal and thoracic outlet compression. Adductor canal, ilioinguinal entrapment and femoral canal compression is an area being explored, but areas that are easily treated with postural change, eg use of a footrest when seated for any period.

Similar findings were found from popliteal compression, with simply standing in a line for long periods, or sitting watching TV with knees straight and legs extended provoking headaches, anxiety, neuropathic symptoms, hypersensitivity to sound and light, sleep disruption etc.

Ilioinguinal entrapment is a common finding, especially in people leaning forward at desks- once again computers the common thread.

During the study, it was trauma to the neck and shoulders that appeared to provoke the most significant symptoms in patients. Sometimes merely examining the thoracic outlet or having the popliteal veins scanned provoked the typical POTS symptoms. The spine is a major factor in triggering TLRs in all the problems of POTS, dysautonomia, migraine and fibromyalgia. This is obvious in trauma especially MVAs, but it also can be occupational, for example in hairdressers, dentists, nurses and supermarket cashiers, or in people working on computers. Increasingly symptoms, including mood disorders can be provoked with the increasing use of smart phones, hand held computers and tablets. Posture is becoming an increasing problem with these devices, and I anticipate increasing problems with spine-driven problems in the future.

Treatment

The treatment of POTS and all these inflammatory problems should I believe be aimed at removing the driving factors rather than looking for a medication to control symptoms. Of course if you cannot stand or arrhythmia is dangerous, or thyroid is destroyed and not functioning, you will need medication. The boundaries are blurring in management as well. Evolving research in nicotinamide (vitamin B3) opens yet another area that may assist the patients with hypermobility by the effect of improved collagen synthesis. At present we have not been able to devise a way of measuring response.

At the end it is at its core quite simple - work out the drivers, especially in the spine and vascular compression, sort out dietary triggers, look at lifestyle, posture, occupational causes, supplement where necessary, and heal what has been damaged, if this is possible.

Many people with these problems have found it has been using weights at gyms, or trauma especially to the shoulders, coccyx and neck that drives their symptoms. The coccyx and neck are innervated by the parasympathetic nervous system –here a neurotransmitter acetylcholine is released, and we have found that injuries to these areas tend to produce fatigue.

Acupuncture, targeted physiotherapy, improved diet lifestyle, occupational and similar changes allow for management based on cause, not symptoms.

High-level acupuncture (especially effective is KIIKO style from Japan) is invaluable in reducing autonomic and inflammatory responses in POTS while causes are chased, and we have completed HRV studies that effectively demonstrate the value of this (yet to be published). There are a few physiotherapists sufficiently skilled to work out the spine and thoracic drivers, but these therapists deal with the mechanical causes. Generic pilates and exercise programs often do more harm than good. There are even fewer dieticians capable of sorting out the food intolerance drivers when present, but they are around.

At present, the research continues, but the knowledge that the popliteal compression can usually be managed by positional change and the thoracic outlet by awareness and improved by suitably trained physiotherapists should provide a useful start for clinicians, while looking at other drivers in each patient.

Conclusion

The current POTS study implied that searching for causes and drivers to POTS, migraine, fibromyalgia and similar problems enables better management opportunities that trying to add drugs, or supplements. This is an evolving science, and I have no doubt further research will unlock even more causes. The introduction of mobile Heart Rate Variability studies has provided a valuable insight into the autonomic chaos that is POTS.

At the end it is at its core quite simple - work out the drivers, especially in the spine and vascular compression, sort out dietary triggers, look at lifestyle, posture, occupational causes, supplement where necessary, and heal what has been damaged, if this is possible.

Acupuncture, targeted physiotherapy, improved diet lifestyle, occupational and similar changes allow for management based on cause, not symptoms.

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