

## Fibromyalgia Review: Remembering What it is and Differentiating What it is Not

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## 1. Abstract

**1.1. Introduction:** Fibromyalgia has become the catch-all disorder for unexplained pain syndromes. As a result, many other disorders (e.g., Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorder) have been misdiagnosed and, as a result, mismanaged. Fibromyalgia is a defined Rheumatological disorder characterized by chronic pain from 11 of 18 tender points typically bilateral and above and below the diaphragm lasting more than 6 months.

**1.2. Methods:** We studied 418 patients previously diagnosed with Fibromyalgia, who presented to five suburban autonomic clinics. All patients submitted to Parasympathetic and Sympathetic (P&S) monitoring as part of the standard of care in these clinics and treated for P&S dysfunction and pain as diagnosed. Data were compiled under HIPAA regulations and statistical analysis performed in SPSS v27.

**1.3. Results:** Only 76 of these 418 patients were diagnosed with Fibromyalgia from Rheumatology and only 64 presented without P&S dysfunction. Of the remaining 342 patients 314 presented with P&S dysfunction.

**1.4. Discussion:** With growing awareness of Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorder (EDS/HSD), we have found that 217 (69.1%) had EDS/HSD. Of the remaining 97 pa-

tients, 77 (24.5%) were traumatized in some way, resulting in Post-Traumatic Stress Disorder, including Traumatic Brain Injury. The remaining 20 patients were idiopathic.

**1.5. Conclusion:** Here we review the strict Rheumatological definition of Fibromyalgia, demonstrate its misunderstanding, and recommend therapy options for treating the disorders that we see as common misdiagnoses.

## 2. Introduction

In Rheumatology, as well as Pain or Physical Medicine and Rehabilitation, Fibromyalgia has become the catch-all disorder for unexplained pain syndromes. As a result, many other disorders (e.g., Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorder) have been misdiagnosed and, as a result, mismanaged. Fibromyalgia is defined by the American College of Rheumatology (1990 [1]) as widespread soft tissue pain syndrome characterized by 11 of 18 tender points typically, bilateral and above and below the diaphragm lasting more than 6 months [1,2] (see Figure 1). A Fibromyalgia diagnosis must exclude other causes of widespread pain with or without fatigue including (1) medications; (2) endocrinopathies; (3) neurologic disorders; (4) malignancies; (5) infections (e.g., Lyme's, Hep B, Hep C, HIV); (6) rheumatic disease such as Rheumatoid Arthritis, Lupus, and Ankylosing Spondylitis;

(7) myopathies; (8) Osteomalacia; (9) tapering steroids due to increased capillary permeability; and (10) other regional pain syndromes, including (A) Ehlers-Danlos Syndrome, (B) Hypermobility Spectrum Disorders, and (C) other connective tissue disorders. Associated features within the Fibromyalgia spectrum include: (1) tension or migraine headache, (2) chemical sensitivity allergic symptoms, (3) Temporomandibular Joint (TMJ) syndrome, (4) irritable bowel, (5) Nondermatomal Sensory Abnormalities, (6) all paresthesia's, (7) Cogan's Syndrome, (8) dry eyes, (9) Vasomotor Rhinitis, (10) vestibular complaints, (11) esophageal dysmotility, (12) Gastroparesis, (13) colonic inertia, (14) autonomic mediated hypotension, (15) Mitral Valve Prolapse, (16) noncardiac chest pain, (17) shortness of breath, (18) Interstitial Cystitis, and (19) Vulvodynia [1]. In the post-COVID era, Long-COVID includes generalized inflammation. While it is understood as an autonomic disorder, it is often misdiagnosed or incorrectly includes a misdiagnosis of Fibromyalgia. Connective tissue disorders, including Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders, are often misdiagnosed or incorrectly include a misdiagnosis of Fibromyalgia. Generalized pain symptoms should be added to the other commonly misunderstood symptoms of Dysautonomia (aka., Autonomic Dysfunction) [4-7] which may include:

1. Small Fiber Neuropathy (SFN, diagnosed with skin biopsy, Sudomotor testing, or P&S testing [viii]) causing abnormal sweating, temperature control disorders, wound-healing difficulties;

2. Orthostatic Dysfunction, including Postural Orthostatic Tachycardia Syndrome (POTS), Orthostatic Intolerance, or Orthostatic Hypotension, all causing lightheadedness and sleep difficulties, depression- or anxiety-like symptoms, ADD/ADHD-like symptoms, OCD-like symptoms, palpitations, shortness of breath, exercise intolerance;

3. Mast Cell Activation Syndrome (MCAS, Mast Cells are immune cells controlled by the Parasympathetic nervous system), causing rashes, hives, food allergies or sensitivities

(including Celiac disorder) and other allergies; GI upset, and women's health difficulties;

4. Auto-Immune Symptoms (over- or persistently active Parasympathetic activity may cause auto-immune like symptoms), especially those without known autoantibodies and those that are inflammatory in nature (adding to pain and being exacerbated by the excessive histaminergic responses, and causing endothelial disorder leading to leaky gut syndrome and more);

5. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), causing fatigue, brain-fog, cognitive and memory difficulties); and

6. Other symptoms of Autonomic Dysfunction; some or all of which potentially lead to headaches, migraines, arthritis-like symptoms, Raynaud's-like symptoms, Venous Pooling, (near-) Syncope, PTSD-like symptoms, difficult to control BP, HR, blood

sugar, or weight, and more. Here, we attempt to show that Fibromyalgia is largely misunderstood. As published [ix], all of these symptoms, including the amplification of the pain (not the pain itself, which may be due to another cause) and syndromes are attributable to Parasympathetic and Sympathetic (P&S) dysfunction. Specifically, two P&S dysfunctions: Parasympathetic Excess (PE, an abnormal Parasympathetic response to stress and other  $\beta$ -Sympathetic reactions) [7,10], and  $\alpha$ -Sympathetic Withdrawal (SW, an abnormal vasopressor reaction causing blood pooling in the lower extremities) [6,11]. Both PE & SW may cause a secondary  $\beta$ -Sympathetic Excess (SE), including high Sympathovagal Balance (SB) at rest causing high resting BP or "Syncope spikes" during stand indicating "adrenalin storms" due to poor cerebral perfusion; with PE being the primary cause of SE. As we have shown with Long-COVID [xii], relieving PE and SW will relieve SE. Relieving these three will relieve POTS, MCAS, inflammatory Auto-Immune Symptoms, ME/CFS, and SFN; and relieving these five symptoms will relieve all the other associated symptoms. Given that relieving PE and SW requires low-and-slow treatment or therapy, treating the other symptoms in the interim is recommended to provide a earlier return of quality of life while we are working to restore P&S balance which includes a return to normal quality of life without much if any medication, depending on history.



**Figure 1:** Tender points that indicate Fibromyalgia [3]

### 3. Methods

Prior to the COVID Pandemic, from 2014 through 2019, 418 patients previously diagnosed with Fibromyalgia were presented to five P&S suburban clinics near Boston, MA; New York City, NY; Philadelphia, PA; Washington DC; and Atlanta, GA. All patients submitted to P&S monitoring as part of the standard of care in these clinics. P&S monitoring includes measuring EKG and respiratory activity to compute P&S activity in response to rest and the three Ewing maneuvers [xiii]: paced breathing at 0.1 Hz, Valsalva maneuvers, and postural change (standing). Based on the monitoring results, PE, SW, and SE were assessed. Data were compiled under HIPAA

regulations and statistical analysis performed in SPSS v27. P&S

treatment includes: for SW) Midodrine (a vasopressor), 2.5 mg tid, Alpha-Lipoic Acid (an anti-oxidant selective for nerves), 600 mg tid, 64 oz to 96 oz of water per day with 5.5 mg to 8.25 mg sodium (for hydration), and compression garments to help relieve blood pooling; and for PE) Nortriptyline 10 qd, 12hrs before waking (as an anti-cholinergic) and low-and-slow exercise.

Also, for those patients not previously prescribed opioids, Low Dose Naltrexone was prescribed for pain, even if they are prescribed other pain relievers, including Cannabinoids.

#### 4. Results

Only 76 of these 418 patients were diagnosed with Fibromyalgia from Rheumatology. Of the whole cohort, 28 patients had only upper or lower trigger point pain (not both). None of these 28 were diagnosed with Fibromyalgia from Rheumatology. Of the 76, only 64 presented without P&S dysfunction. Of the remaining 342 patients 314 presented with P&S dysfunction (PE and SW). Of the remaining 28 patients, 19 had only SW (10 patients, with normal BP and HR response to stand indicating that SW was not masked) or only PE (9 patients). The other 9 were found to meet the Rheumatological definition of Fibromyalgia. All patients contracted the COVID-19 virus or suffered COVID-19 vaccine injury. Only 169 patients had time to treat and normalize their P&S activity prior to contracting COVID. COVID set all other patients back, including returning previous symptoms, and adding more. Of the 169, 146 (86.4%) report total relief of symptoms, with only occasional flares of symptoms due to high stress situations, whether personal or medical. The remaining 23 (13.6%) had set-backs due to other causes, including Lyme disease or other severe illnesses, concussion, injury or surgery, or emotional traumas. Of the patients that contracted COVID before normalizing their P&S activity, approximately the same percentage (> 80%) reported feeling better than before P&S treatment started. The problem with specifying this percentage is that daily stresses may cause flares or patients do not realize their improvements and if loved ones do not accompany the patient, they tend to under-report any improvements.

#### 5. Discussion

With growing awareness of Ehlers-Danlos Syndrome/Hypermobile Spectrum Disorder (EDS/HSD), we have found that 217 (69.1%) had EDS/HSD. Of the remaining 97 patients, 77 (24.5%) were traumatized in some way, resulting in Post-Traumatic Stress Disorder, including Traumatic Brain Injury. The remaining 20 patients were idiopathic. Fibromyalgia, as its definition states, is tender point pain and has proven itself to be unassociated with inflammatory conditions in its purest sense. Patients who have Hypermobility with or without definitive EDS, Dysautonomia, especially with SFN or MCAS, may present with widespread total body pain. The pain from these are largely inflammatory in nature. They frequently complain of pain and burning throughout the skin and hair and literally the entire body with or without tender point pain that

may or may not be masked. -It seems apparent that Fibromyalgia, as it is largely diagnosed, is merely a portion of the Dysautonomia Spectrum and not the opposite. This is becoming more apparent in the Long-COVID era as Dysautonomia is becoming more well recognized. Patients diagnosed with Diabetes or Hypermobility typically present with chronic pain with burning all over which is frequently due to SFN. Patient's present with autoimmune disease that is often overlooked and have inflammatory myopathy, arthropathy, or tendinopathy which mimics pain all over. Clearly in Dysautonomia there are varieties of  $\alpha$ SW and  $\beta$ SE as well as PE that are typically seen in the patients that are previously misdiagnosed as simply having "Fibromyalgia." They are treated with SSRIs, in particular Cymbalta (Duloxetine), Savella (Milnacipran HCl) or Gabapentin (Neurontin) or pre-GABA. Occasionally inflammation (Rheumatoid Arthritis, Lupus, Myositis) causes these nerves to be over-active amplifying the neuralgia or paresthesia that is characteristic of SFN. It also affects, and amplifies, the Sympathetic innervation to the periphery, causing abnormal and excessive vasoconstriction, leading to poor wound healing, abnormal sweating, and poor temperature control, which tends to add to pain. The physiologic drop in body temperature while sleeping leads to a component of morning stiffness. Fibromyalgia patients, by definition, do not have any stiffness they have tender point pain while Hypermobile Dysautonomia, MCAS patients will typically have 6 or 12 hours of stiffness which differentiates them from Rheumatoid Arthritis, Psoriatic Arthritis or Lupus, which typically have 30-90 minutes of morning stiffness. It is well known that pain is stress. The Sympathetic nervous system mediates stress, inflammation, histaminergic responses, etc., and thereby pain. SE, in cases of pain amplifies pain by exaggerating the pain, inflammatory, histaminergic responses or other responses that lead to pain. In the cases of PE, PE causes SE. The amplified pain associated with SE due to PE often is difficult to manage because the therapy tends to address more the SE rather than the PE. The previously diagnosed cases of Fibromyalgia that were actually EDS/HSD all tested positive for PE, they all reported little relief from pain except for very high doses of multiple pain treatments and therapies. Pain Amplification Syndrome patient reports tender points in the usual Fibromyalgia places, however, also reports pain in the placebo-controlled points such as the Volar Forearm, the Forehead and the Thumbnail. In general, amplified histamine and inflammatory responses which may add to pain, and amplified anxiety-like symptoms which may add to the perception of pain may involve PE underlying SE. PE also leads to poor cerebral perfusion and the perfusion of all structures above the heart, including the muscle spasms that underlie "coat-hanger" pain which may lead to tension headache. Poor cerebral perfusion itself is also a cause of headaches as well as migraine. SW contributes to the pain caused by PE by contributing to poor cerebral perfusion. SW also adds to pain by causing Raynaud's-like symptoms of cold or discolored

hands and feet due to venous blood pooling in the feet and poor circulation above the heart to the hands. Laxity of joints associated with EDS/HSD is a source for inflammation and associated pain, including early Osteoarthritis, wrist and elbow joint pain, and knee pain with minimal or no use due to patellofemoral laxity which also leads to early Osteoarthritis. Easy bruising in connective tissue disorders, likely due to impaired collagen in endothelial cells is a source of pain. Inflammation caused by joint laxity causes pain every time a joint is moved. Without the ability to independently and simultaneously measure P&S activity (most measures of autonomic dysfunction only measure total autonomic function and force assumption and approximation to theorize P&S dysfunction) PE is not detected. It is, however, seen as only SE. The problem is that treating SE all too often exacerbates the condition because SE is a compensatory mechanism used by the body to attempt to restore proper perfusion and counter the other effects of PE. Therefore, even though the patient may diligently follow the prescribed treatment regimen, the body defeats the therapy. This all too often degrades the relationship between provider and patient, further exacerbating the condition.

## 6. Conclusion

EDS/HSD is still a little-known genetic disorder that requires a multi-system, detailed assessment of the patient, including specific P&S testing to differentiate from Fibromyalgia and many other symptoms that are perceived in isolation, rather than as part of a greater whole. It is another condition that must be ruled-out before a Fibromyalgia diagnosis is determined. Similarly, other causes of P&S dysfunction, such as PTSD and Long-COVID, may also include symptoms of Fibromyalgia. However, these are more pervasive, multi-system disorders that, like EDS/HSD, when P&S dysfunction is relieved will also relieve the Fibromyalgia symptoms. With P&S monitoring all P&S (autonomic) dysfunctions are treatable [8,14], including the symptoms of Fibromyalgia, whether it is a primary disorder or secondary to the cause of P&S dysfunction.

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