Is It Really Fibromyalgia? Recognizing Mast Cell Activation, Orthostatic Tachycardia, and Hypermobility

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Is It Really Fibromyalgia? Recognizing Mast Cell Activation, Orthostatic Tachycardia, and Hypermobility

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PATIENT SCENARIOS

Scenario 1: 38-year-old male presents with widespread severe pain not improved by anything other than Oxycontin, which "only takes the edge off." He also reports severe irritable bowel with frequent diarrhea, gluten intolerance, flushing, itching and hives, and chronic sinus congestion with frequent infections. He does not sleep well and is constantly fatigued. When he tries to exercise or participate in social activities, his hives will flare and he 'crashes' for several days due to flare of all symptoms. Pain is rated 8-9/10 most of the time. Using the 2016 diagnostic criteria for fibromyalgia (FM), his Widespread Pain Index (WPI)=19/19 and Symptom Severity Score (SSS) =10/12 (see Figure 1 for items in WPI and SSS).

Scenario 2: 14-year-old female presents with widespread pain, anxiety, and fatigue that prevents her from attending school. Symptoms began 2 years ago after forced bedrest due to a severe flu. Her primary complaint are the debilitating fatigue and anxiety attacks, but she also reports headaches, brain-fog, episodes of syncope, tachycardia, difficulty sleeping, activity/exercise intolerance, and cold hands and feet. Pain 4/10 most times, 8/10 during flares; FM WPI=5/19 and SSS=11/12.

Scenario 3: 42-year-old female presents with widespread, migrating pain, headaches, and fatigue that interferes with her ability to work as an administrative assistant. As a child, she was clumsy and frequently bumped into things or fell, twisting ankles or causing bruises. She has difficulty sleeping because it is difficult to get comfortable in bed. Previous physical therapy attempts to get her to exercise have increased pain. Pain is generally 6/10. Her WPI=14/19 and SSS=7/12.

INTRODUCTION

Fibromyalgia is a disorder characterized by chronic, widespread musculoskeletal pain and associated with severe fatigue, sleep disturbance, depression, gastrointestinal disorders, anxiety, paresthesias, headaches, and other signs and symptoms listed in Table 1.[1] Management of people with fibromyalgia is challenging, involves high utilization of heath care resources, and is not successful in reducing the huge costs in money, productivity, and quality of life.[1,2] People with FM still report poorer quality of life and are more likely to be disabled than people with other chronic widespread pain conditions.[2] Fibromyalgia affects 2% to 6% of the population in the United States; 10% of those patients access physical therapy in any given year[1] and 30% access some physical treatment (physical therapy, acupuncture, massage) in a 3-month period.[2] Though a number of interventions show some benefit, studies show that patients are often dissatisfied with their health care management.[3]

The pathophysiology of FM is not fully understood. For several decades, FM has been considered the prototypical 'central sensitization' condition, where the central nervous system increases sensitivity of many organ systems. Increased sensitivity results in hyperalgesia and allodynia of a variety of tissues, resulting in increased pain sensitivity (eg, headaches or migraines, pelvic pain, temporomandibular pain, myofascial trigger points, arthralgias, interstitial cystitis, etc) as well as nonpain complaints such as brain fog, irritable bowel, chronic fatigue, poor quality sleep, chemical sensitivity, anxiety, etc. See Fleming and Volcheck[4] for discussion of central sensitization.

More recently, research has hypothesized that the pathophysiology of FM is driven by neurogenic inflammation, where afferent nociceptive neurons are activated antidromically (towards the periphery), causing release of inflammatory mediators at the peripheral nerve endings. While neurogenic inflammation normally contributes to the healing response by initiating inflammation, excessive inflammation leads to peripheral and central sensitization, which creates a positive feedback loop of inflammation and nociception. Peripheral neurogenic inflammation contributes to the diffuse edema and neurogenic flare often seen in FM. Peripheral neurogenic inflammation involving the sympathetic nervous system could contribute to other organ system involvement, such as irritable bowel, migraine, or anxiety. Central neurogenic inflammation is also present in FM and may contribute to central sensitization and involvement of the hypothalamic pituitary adrenal axis, which would lead to sleep disturbance and reactivity to emotional stress. See Littlejohn et al,[5] and Chiu et al,[6] for detailed discussions of neurogenic inflammation in FM.

One of the challenges with FM is the lack of a definitive diagnostic test. In 1990, the American College of Rheumatology adopted criteria requiring at least 11 of 18 specified tender points to demonstrate widespread pain[7]; however, these criteria were neither reliable nor specific. In 2010, the diagnostic criteria were revised to reflect the belief that FM was due to central sensitization, and was often associated with other symptoms such as fatigue, poor sleep, cognitive complaints, headaches and depression; other diagnoses that could explain the signs and symptoms had to be ruled out.[8] In 2016, the diagnostic criteria were modified again, and are shown in Figure 1; they include a Widespread Pain Index (WPI) score that must include pain in 4/5 body regions, a SSS, and the presence of symptoms for at least 3 months. There is no longer a requirement to rule out other conditions that may explain the findings.[9]

Signs and symptoms of FM overlap with those of many other conditions that have widespread, multisystem involvement.[10] Three such conditions will be discussed here: Mast Cell Activation Syndrome (MCAS), Postural Orthostatic Tachycardia Syndrome (POTS), and Hypermobility Spectrum Disorder ([HSD], previously known as Joint Hypermobility Syndrome) which, constitute a common triad of comorbidities.[11] Table 1 shows the substantial overlap in signs and symptoms for these 3 conditions with FM.[8,12-15]

MAST CELL ACTIVATION SYNDROME

Mast cells are a part of the body's inflammatory and allergic response and are found in almost every tissue in the body. In MCAS, mast cells are overactive but not overabundant (as in mastocytosis, which is a rare condition).[16,17] The mediators released trigger inflammatory responses in various systems, leading to signs and symptoms that overlap extensively with FM (see Table 1).[18] Studies show that MCAS is common in conditions associated with central sensitization, such as FM, chronic fatigue, irritable bowel, pelvic pain, vulvodynia, and migraine.[18,19] Neurogenic inflammation may provide the link between central sensitization

2016 Fibromyalgia Diagnostic Criteria

Widespread pain index (WPI)

Where has the patient had pain *in the past week*,? (check all that apply)

Left upper region (1) ☐ *L jaw* ☐ L shoulder girdle ☐ L upper arm ☐ L lower arm	**Right upper region (2)** ☐ *R jaw* ☐ R shoulder girdle ☐ R upper arm ☐ R lower arm	**Axial region (5)** ☐ Neck ☐ Upper back ☐ Lower back ☐ *Chest* ☐ *Abdomen*
Left lower region (3) ☐ L hip (buttock/trochanter) ☐ L upper leg ☐ L lower leg	**Right lower region (4)** ☐ R hip (buttock/trochanter) ☐ R upper leg ☐ R lower leg	

Total: _____ WPI score (add up boxes checked, 0-19)

_____Number of regions checked (excluding items in italics); use this for criterion #2.

Symptoms Severity Score (SSS)

Rate the severity for each of the following symptoms *for the past week*:

	0=No problem	1=slight or mild problem, often mild or intermittent	2=moderate, considerable problem, often present	3=severe, pervasive, continuous, life-disturbing
Fatigue	☐	☐	☐	☐
Waking unrefreshed	☐	☐	☐	☐
Cognitive symptoms	☐	☐	☐	☐

Has the patient been bothered by any of the following *in the past 6 months*?

	0=No problem	1=Problem
Headaches	☐	☐
Pain or cramps in lower abdomen	☐	☐
Depression	☐	☐

Total SSS: _____(0-12)

Fibromyalgia Severity (FS) scale is the sum of WPI and SSS: _____

A patient satisfies the 2016 fibromyalgia diagnostic criteria if the following 3 criteria are all met, *independent of whether other diagnoses contribute to these symptoms*.

☐ **1. Criterion 1 is met if EITHER:** ☐WPI ≥ 7 and SSS ≥ 5 **OR** ☐ WPI 4-6 and SSS ≥ 9

☐ **2. Generalized pain: met if pain is in 4/5 regions (not including items in italics)**

☐ **3. Symptoms have been generally present ≥ 3 months**

Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum.* 2016;46(3):319-329.

Figure 1. 2016 Diagnostic criteria for fibromyalgia.[9]

and mast cell activation, as the inflammatory mediators released peripherally by nociceptive neurons in neurogenic inflammation cause histamine release from mast cells, which leads to peripheral sensitization in a variety of tissues. Mast cell activation has also been reported in the central nervous system in FM, contributing to central sensitization.[19,20] Mast cells are prevalent in the gut and skin, explaining common complaints of MCAS. Mast cells are also very sensitive to activation of the hypothalamic pituitary-adrenal axis, hence are responsive to emotional stress, helping to explain why stress exacerbates so many symptoms.[21,22]

The current diagnostic criteria for MCAS are (1) typical clinical symptoms (see Table 1), (2) ≥ 20% increase in serum tryptase during or after a symptomatic period, and (3) response of clinical symptoms to histamine receptor blockers. Mast Cell Activation Syndrome is not yet well recognized in the United States and tryptase measurements are technically difficult, making definitive diagnosis challenging and frustrating for patients.[17]

Table 1. Comparison of common signs and symptoms in Fibromyalgia, Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome and Hypermobility Spectrum Disorder. Compiled from multiple references.[8,12-15]

System	Health Issues	FM	MCAS	POTS	HSD
Neurological	• Central sensitization, hyperalgesia	X	X	X	X
	• Headaches, migraines, dizziness	X	X	X	X
	• Syncope or presyncope	X	X	X	X
	• Paresthesias and nerve compression disorders	X	X	X	X
	• Restless leg syndrome	X	X	X	X
	• Motor delay (in children)				X
	• Proprioceptive and motor control deficits, clumsiness, frequent falls, trips or bumping into things	X			
Cognitive	• Anxiety and panic disorder	X	X	X	X
	• Memory or concentration problems	X	X	X	X
	• Depression	X	X	X	X
Immune	• Excessive inflammatory response	X	X	X	X
	• Chemical and environmental sensitivities (including meds)	X	X	X	X
	• Frequent infections		X	X	
Autonomic	• Dysautonomia, palpitations, tachycardia	X	X	X	X
	• Sweats	X	X	X	
	• Raynaud syndrome	X	X	X	X
Cardiopulmonary	• Varicose veins		X	X	X
	• Diffuse or migratory edema	X	X	X	X
	• Deconditioning	X	X	X	X
	• Short of breath	X	X	X	X
Musculoskeletal	• Frequent sprains, subluxations and dislocations				X
	• Chronic joint pain	X	X	X	X
Soft tissues	• Tendinitis, bursitis, synovitis, tenosynovitis, fasciitis or tendon ruptures	X	X		X
	• Trigger points, muscle spasm	X		X	X
	• Muscle strain				X
Gastrointestinal	• Irritable bowel syndrome, diarrhea, food sensitivities	X	X	X	X
	• Abdominal pain, bloating	X	X		
	• Gastroparesis/constipation	X			X
	• Gastroesophageal reflux, chronic gastritis, heartburn	X	X		X
	• Hernias (all types) and organ prolapse				X
Dermatologic	• Hyperextensible and fragile skin				X
	• Slow healing or scarring, poor wound healing		X		X
	• Easy bruising	X	X		X
	• Dermatographia	X	X		
	• Flushing, pruritis, rashes	X	X	X	X
Urogenital	• Urinary incontinence	X	X		X
	• Prolapsed bladder or uterus			X	X
	• Urinary tract infections	X	X		X
	• Dysmenorrhea, endometriosis, vulvodynia, pelvic pain, painful intercourse	X	X		X
Nonsystem	• Female predominance	X	X		X
	• Insomnia, sleep disturbance	X	X	X	X
	• Chronic fatigue	X	X	X	X
	• Exercise intolerance	X	X	X	X
	• Symptoms worse in the morning	X		X	
	• Symptoms aggravated by stress	X	X	X	

Abbreviation: FM, Fibromyalgia; MCAS, Mast Cell Activation Syndrome; POTS, Postural Orthostatic Tachycardia Syndrome; HSD, Hypermobility Spectrum Disorder

Management of Mast Cell Activation Syndrome

Management of MCAS emphasizes patient education regarding triggers and trigger avoidance. Key triggers include rapid temperature changes (including during exercise), ultraviolet radiation, histamine-rich or histamine-releasing foods, mechanical irritation, ethanol, narcotics, some nonsteroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors, and beta-blockers.[23] Stress is also a common trigger that should be decreased; interestingly, mindfulness meditation is shown to decrease neurogenic inflammation.[24] Although there is no research yet supporting low histamine diets for reducing inflammatory response in MCAS, some patients report that dietary control is helpful.[22] Pharmacological management emphasizes histamine blockers; medications that exacerbate mast cell activation should be avoided.[18,23]

Scenario 1

This patient presented with signs of widespread inflammation involving peripheral and central nervous systems, gut and skin typical of MCAS; because of the challenge in confirming a diagnosis of MCAS, his diagnosis is presumed. Neurogenic inflammation triggers peripheral and central sensitization and key signs and symptoms of FM. In this patient, mast cell activation may have exacerbated the systemic inflammatory response, and contributed to flares in response to exercise, stress, and certain foods. Furthermore, opiates and NSAIDs taken to reduce pain may, in fact, have aggravated his inflammatory response.

Because his gastrointestinal symptoms were so intense, the patient chose to start by trying a 'low histamine' diet, and when he returned in 2 weeks, reported feeling "90% better" with minimal pain, improved energy, and tolerance to activity. He had voluntarily discontinued all opiate medications. Fibromyalgia SSS 4/12; WPI 5/19. His physical therapy program continued with pain neuroscience education emphasizing self-management with cognitive behavioral approaches, and a gradually progressed aerobic exercise program to address deconditioning, enhance descending inhibition pathways,[25] and potentially stabilize mast cell activity in muscles.[26]

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

Postural orthostatic tachycardia syndrome is a type of dysautonomia in which inadequate venous return to the heart evokes a strong sympathetic tachycardia response. Prevalence of POTS is reported to be up to 1%, but it is likely underdiagnosed.[27] Postural orthostatic tachycardia syndrome affects women 5 times more often than men and most often affects women during adolescence and childbearing age. Although there is little research, experts suggest that it may be common in FM.[28] Postural orthostatic tachycardia syndrome is formally diagnosed using a tilt-table test monitoring both heart rate and blood pressure during 5 minutes of resting supine and for 10 minutes after the patient transitions to upright; a Stand Test can be performed by having the patient stand quickly and keep still, without fidgeting.[27,29] Sustained heart rate increases ≥ 30 bpm (≥40 bpm in children) within 10 minutes of moving from supine to standing, without BP drop of 20/10 mmHg indicate POTS. Other signs and symptoms of POTS overlap substantially with FM (see Table 1). Multiple pathophysiological processes lead to the presentation: decreased venous return causes tachycardia, which leads to anxiety; decreased circulation to the brain results in lightheadedness, anxiety, brain fog, and syncope; frequent sympathetic response causes fatigue.[27,30] Inappropriate autonomic response to exercise leads to exercise intolerance, or severe fatigue as a result of low levels of exercise.[31] Symptoms are often initially triggered by a physical stressor that results in forced rest, such as surgery, pregnancy, illness, or injury. See Arnold et al,[27] for more detail about POTS diagnosis and pathophysiology.

Management of Postural Orthostatic Tachycardia Syndrome

Physical therapy plays a key role in management of POTS. Education about POTS self-management should address fatigue, sleep disturbance, exercise intolerance, anxiety, and other symptoms. Patients with POTS may benefit from increasing fluid and electrolyte consumption, compression stockings, strategies such as ankle pumps to improve venous return, and may need to lie supine with feet elevated to manage symptoms of syncope or anxiety. Individuals with low exercise tolerance may need to begin exercising with recumbent lower extremity strengthening exercises to facilitate venous return and gradual progression to aerobic exercise in a recumbent position with gradual progression to upright. Psychological and behavioral approaches such as stress management, pacing, and cognitive behavioral therapy are often also beneficial.[32-34] Although no medications have been approved for POTS, some are recommended off-label; medications that aggravate symptoms should be avoided. See Strassheim et al,[32] and Raj,[35] for excellent overviews of POTS management.

Scenario 2

This is a patient with POTS, which often presents initially in adolescent females, especially after forced bedrest as with this patient whose symptoms began after an illness. The stand test showed heart rate change from 72 bpm to 125 bmp with standing, and provoked symptoms of anxiety, pre-syncope, and headache. Fatigue results from inappropriate autonomic responses aggravated by deconditioning and sleep disturbance. Activity and exercise intolerance is common, especially in response to exercise in the upright position, which places additional stress on venous return.

This patient's program emphasized education regarding POTS, the effect of position on venous return and how this can contribute to syncope and anxiety, the importance of hydration, and salt intake to maintain blood volume. She was advised to lie supine with the feet elevated when she experienced pre-syncope or anxiety. She was put on a graded exercise program starting with supine lower extremity strengthening (to improve venous return) and very low-level aerobic exercise using the recumbent bike. After 6 months, she had returned to full days at school, was participating in gym, and had no episodes of syncope or anxiety. She continued to have episodes of severe fatigue after increased activity or emotional stress. She no longer met the diagnostic criteria for FM. She reported pain typically 0/10 except for intermittent headaches, WPI = 0/19 and SSS = 4/12. She was discharged to an ongoing graded exercise program.

HYPERMOBILITY SPECTRUM DISORDER

Research suggests that HSD is a common comorbidity of FM, with 47%[36] to 65%[37] of patients with FM demonstrating HSD; some have proposed that HSD may often be incorrectly diagnosed as FM.[10,38] Recently, HSD has been recognized as the most common heritable connective tissue disorder, possibly affecting up to 10% of the United States population, affecting children equally but women past puberty 2 to 8 times more often than men.[39] The

primary signs and symptoms of HSD, beyond widespread hypermobility, are listed in Table 1, and clearly overlap extensively with FM. See Tinkle et al[39] for a detailed discussion of HSD. Multisystem involvement reflects the fact that most connective tissues can be affected and not just joints. Symptoms may be triggered by musculoskeletal trauma or overuse, often by minor stressors. Symptoms may flare after forced rest due to surgery, illness, pregnancy, or injury; a possible mechanism is through decreased muscle tone increasing joint instability.[38,40] The pathophysiology is not yet understood; unlike other forms of Ehlers Danlos Syndrome (EDS), no genetic marker has yet been identified[41] and some suggest that connective tissue integrity is compromised by excessive mast cell activity.[11,12]

The diagnostic criteria of HSD have also evolved in the past few years. In an effort to identify a genetic marker, diagnostic criteria for hypermobile EDS (hEDS, available at https://ehlers-danlos.com/wp-content/uploads/hEDS-Dx-Criteria-checklist-1.pdf)[42] were made deliberately restrictive and exclude many patients who were previously diagnosed with Joint Hypermobility Syndrome. Consequently, HSD has been defined as generalized joint laxity associated with some of the other diagnostic criteria for hEDS, but not enough to meet the new, stricter criteria for hEDs.[42] Joint hypermobility is assessed using the 9-point Beighton score: hyperextension of elbows or knees ≥ 10º, touching the thumb to forearm, hyperextension of 5th MCP ≥ 90º, and trunk flexion placing palms on the floor with knees extended. Prepubescent children must score ≥ 6/9, puberty to 50 years must score ≥ 5/9, and people over 50 years must score ≥ 4/9. Because injuries my compromise mobility in some joints, people who score 1 point below the cut-off can add 1 point if they answer Yes to ≥ 2 items on the 5-item questionnaire about historical hypermobility.[41-42]

Management of Hypermobility Spectrum Disorder

Physical therapy is key to management of HSD. Patient education should emphasize injury prevention through proper body mechanics, joint protection, posture, and ergonomics. Identification of aggravating activities, positions, or muscle length-strength imbalance is critical; gravity, alone, may cause joint subluxation. Migrating pain is due to overload of fragile connective tissue, tight muscles pulling on loose joints, trigger points, poor body mechanics, and motor control. Exercise should include proprioceptive and motor control training, followed by strengthening of stabilization muscles and graded aerobic exercise. Exercises need to be progressed more gradually in patients with HSD due to connective tissue weakness and increased time to gain strength.[39] Orthotics are often helpful for improving alignment of the lower extremities, but evidence for bracing is weak and experts recommend bracing only during flares.[40] Sleep hygiene can help manage sleep disruption; patients may be hypersensitive to pressure from the bed and may benefit from experimenting with bed surfaces. Cognitive behavioral approaches and pain self-management are also helpful.[34] There are no medications, currently, that address the pathophysiology of HSD; medications can be used to address symptoms of pain and inflammation.[38]

Scenario 3

This is a patient with HSD. Clumsiness and frequent injury reflect the proprioceptive and motor control deficits common with HSD. Headaches are typical of cervical instability and secondary trigger points in muscles overworked trying to stabilize hypermobile joints. Fatigue and brain fog are likely due to sleep disturbance, which is commonly due to discomfort from whatever body part contacts the bed. Her poor response to exercise in the past reflects fragile tissues that are unable to tolerate standard exercise programs and progressions.

Her program emphasized patient education regarding HSD, posture, body mechanics, self-management of trigger points, and the fact that minor physical stressors could cause pain. She began gentle proprioception and motor control exercises to improve stabilization of her cervical spine. She also began sleeping on a featherbed to distribute body weight while sleeping. After 3 months, her headaches were gone. She was sleeping better, but still not waking refreshed. She had intermittent migrating pain that she was typically able to attribute to specific postures or activities. Pain was generally 2/10 with occasional flares up to 5/10. She no longer met the diagnostic criteria for FM: WPI=3/19 and SSS=3/12. She was discharged with an ongoing exercise and pain self-management program.

CONCLUSION

These patient scenarios demonstrate research that shows HSD co-exists with FM or is misdiagnosed as FM[36,37] and that MCAS presents with FM-type symptoms.[12] Little research has been done to measure the co-morbidity of POTS with FM. Mast cell activation syndrome, POTS, and HSD often present as a triad and have many overlapping signs and symptoms.[11] However, MCAS has a dominant inflammatory presentation, POTS has primarily autonomic signs and symptoms, and HSD leads to mechanical stresses on fragile tissues. While the additional diagnoses do not cure FM, patients are often reassured to understand factors underlying what can seem like random and unrelated symptoms. Patients with HSD are often relieved to learn that there is a reason for their hypersensitivity and frequent injuries.[43] Patients with POTS are often relieved to have an explanation for anxiety attacks, syncope, and extreme intolerance to (upright) exercise and activity (personal observation). Patients with MCAS are often relieved to make sense of all of their various symptoms affecting multiple tissues and organs (personal observation).

Physical therapy is key to managing HSD[34,38,40] and POTS,[44] recognition and management of these conditions is critical. Looking for and managing MCAS, POTS, and HSD is not a magical solution for treating patients with FM. However, addressing these other conditions can help to decrease the overall symptom load, inflammatory state, and neural sensitization that contribute to high levels of morbidity in FM.

PATIENT AND CLINICIAN RESOURCES

- The National Fibromyalgia & Chronic Pain Association, at https://www.fmcpaware.org/
- The American Fibromyalgia Syndrome Association, Inc, at http://www.afsafund.org/
- Mast Cell Action, at https://www.mastcellaction.org/about-mcas
- The Mastocytosis Society, at https://tmsforacure.org/
- PoTS UK, at www.potsuk.com
- Standing Up To POTS, at http://standinguptopots.org
- The Ehlers-Danlos Society, at www.ehlersdanlos.com
- HMSA: Hypermobility Syndrome Association, at www.hypermobility.org

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