

Chronic Fatigue Syndrome: From Chronic Fatigue to More Specific Syndromes

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Abstract

In the last decade, a group of chronic disorders associated with fatigue (CDAF) emerged as the leading cause of chronic fatigue, chronic pain, and functional impairment, all of which have been often labeled in clinical practice as chronic fatigue syndrome (CFS) or fibromyalgia. While these chronic disorders arise from various pathophysiologic mechanisms, a shared autoimmune or immune-mediated etiology could shift the focus from symptomatic treatment of fatigue and pain to targeted immunomodulatory and biological therapy. A clinical paradigm shift is necessary to re-evaluate CFS and fibromyalgia diagnoses and its relationship to the CDAF entities, which would ultimately lead to a change in diagnostic and therapeutic algorithm for patients with chronic fatigue and chronic pain. Rather than uniformly apply the diagnoses of CFS or fibromyalgia to any patient presenting with unexplained chronic fatigue or chronic

pain, it may be more beneficial and therapeutically effective to stratify these patients into more specific diagnoses in the CDAF group.

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Introduction

In the last decade, much has been written in the scientific literature about a group of chronic disorders associated with fatigue (CDAF) originating from various etiologies, which causes a wide variety of multi-systemic symptoms, and ultimately results in chronic fatigue, chronic pain, and impaired functional level. Patients with CDAF are commonly labeled with chronic fatigue syndrome (CFS) and/or fibromyalgia, since the diagnostic criteria can be easily applied to most patients with CDAF. Although CDAF encompasses a number of diagnostic entities, each with specific physiologic basis, all disorders in the CDAF group could also fit under the diagnostic criteria of CFS due to the presence of the following key features: chronic fatigue, chronic pain including headaches, sleep disturbance, mood disorder, cognitive complaints, post-exertional malaise, exercise intolerance, and inability to maintain a pre-illness level of functioning [1].

Clinical Features

Like CFS, CDAF typically begins after a precipitating event, such as a viral, bacterial, or fungal infection, a major or minor surgery or surgical procedure, a motor vehicle accident, concussion, pregnancy, immunization, or after a period of severe physical or mental stress. In some cases, no precipitating factor can be identified, but there may be a family history of similar symptoms and syndromes in the first-degree family members, suggesting a genetic component. At the onset of illness, patients with CDAF are typically diagnosed with “CFS,” or “fibromyalgia” by their primary care physician. Eventually and often after years of seeking answers and better treatment, the patients are referred to other specialties for evaluation of various multi-systemic symptoms. In fact, studies have shown that almost 50% of patients with the original diagnosis of CFS are actually misdiagnosed when they are reevaluated by specialists in CFS clinics [2]. At this time, a diagnosis of CFS may be replaced with one of the diagnoses in the CDAF group. These diagnoses may include one or more of the following entities:

- Postural Orthostatic Tachycardia Syndrome
- Neurocardiogenic syncope
- Small fiber neuropathy
- Undifferentiated Connective Tissue Disease
- ASIA syndrome
- Post-treatment Lyme Disease Syndrome (aka “chronic Lyme disease”)
- Hypermobility Ehlers-Danlos Syndrome
- Mast Cell Activation Syndrome
- Seronegative anti-phospholipid syndrome

Diagnosis

Each of these diagnostic entities is characterized by manifestations specific to the entity in addition to the original key features of the CFS criteria (Table 1) [3–11].

Similar to CFS, these disorders can be vastly misdiagnosed with psychiatric illness, despite the presence of clinical features pointing toward a physiologic cause [3–11]. A significant number of patients with both CDAF and CFS have abnormal markers of autoimmunity, inflammation, or immunologic function [3–15]. Current studies are focusing on beta adrenergic and muscarinic antibodies as potential targets in the diagnosis and treatment of CFS [12], but commercial test-

ing of these antibodies has not been made available in the United States.

Objective diagnostic findings include evidence of the orthostatic intolerance on a tilt table test, autonomic dysfunction and small fiber neuropathy on the autonomic function tests, hypovolemia on blood volume testing, and abnormalities on the functional MRI, SPECT, or PET scan of the brain (conventional MRI of the brain is typically unremarkable or demonstrates non-specific or incidental findings). While the underlying etiology of these disorders is not based on the psychological or psychiatric causes, many patients can develop comorbid anxiety and depression that may be secondary to chronic illness or as part of the key features of the underlying pathophysiology.

Therapeutic Approach

Typically, patients are evaluated by numerous clinicians from various specialties, including neurology, cardiology, rheumatology, gastroenterology, allergy and immunology, otolaryngology, sleep medicine, psychiatry, and psychology. Often patients are treated with symptom-based approach after common diseases in each specialty are excluded from the differential diagnosis. Patients with CDAF usually undergo extensive diagnostic workup that is either unremarkable or shows mild abnormalities that do not fit into a specific diagnostic entity. Physical therapy, occupational therapy, psychotherapy, cardiac rehabilitation program, and chronic pain rehabilitation programs are often employed with a variable degree of success. Alternative therapies in the form of chiropractic care, acupuncture, massage therapy, acupressure, and reflexology are commonly implemented by the patients in order to obtain relief from various chronic symptoms that interfere with their daily life. Naturopathic and integrative medicine with a variety of treatment protocols consisting of vitamins, mineral, supplements, and herbs have become popular in the patient community, but less conventional therapies, such as hyperbaric oxygen and intravenous hydrogen peroxide, are also gaining momentum despite a lack of evidence-based studies on the efficacy of such therapies. Some of the alternative therapies may be actually harmful due to possible allergic reactions or other adverse effects, and physicians from various specialties need to be prepared to discuss the risks and benefits of nonconventional therapies with their patients.

Table 1. Chronic disorders associated with fatigue: clinical features, diagnosis, and treatment

Chronic disorder	Clinical features	Diagnostic criteria	Diagnostic tests	Common treatment
POTS	Orthostatic intolerance, postural tachycardia, fatigue, dizziness, headaches, nausea, muscle pain	Greater than 30 bpm (or 40 bpm in teens) increase in HR on TTT without OH	TTT Supine and standing BP/HR Autonomic function tests	Beta blockers, fludrocortisone midodrine, high fluid/sodium intake
NCS	Fainting Orthostatic intolerance	LOC on TTT associated with abrupt drop in BP on TTT	TTT Autonomic Function tests	Fludrocortisone Midodrine Beta blockers High fluid/sodium
SFN	Neuropathic pain, Numbness/tingling/burning/itching Allodynia/dysesthesia	Reduced ENFD/SGNFD on skin biopsy Decreased sweat output on QSART	QSART/TST/skin biopsy	Gabapentin Pregabalin Amitriptyline Duloxetine Topical lidocaine
UCTD	Joint pain, muscle pain Fatigue, headache	Clinical symptoms, abnormal markers of autoimmunity, not sufficient for a diagnosis of defined CTD	ANA, RF, CRP, ESR, other positive antibodies	Corticosteroids, hydroxychloroquine, NSAIDs
ASIA syndrome	Myalgia, myositis, arthritis, arthralgia, chronic fatigue, cognitive impairment	Exposure to external stimuli (infection, vaccine, silicone)	ANA, ESR, CRP, RF. Other positive antibodies, HLA typing	Removal of inciting stimuli if possible
PTLDS	Chronic fatigue, joint pain, cognitive disturbance	Persistent symptoms after a Lyme infection despite treatment with antibiotics	None specific to PTLDS; Lyme antibodies may be positive	Long-term antibiotics do not appear to be beneficial
hEDS	Joint hypermobility, joint pain, fatigue, headaches, easy bruising, sleep disturbance	2017 diagnostic criteria for HEDS	Beighton score	Physical therapy, orthotics
MCAS	Flushing, itching, hives, fatigue, fainting, headaches, diarrhea, constipation, nausea, bone pain, tachycardia, insomnia	Episodic symptoms consistent with mast cell mediators release, improvement with anti-mediator therapy	Serum tryptase, 24-h urine N-methylhistamine, 24-h urine PGD-2, elevation of mediators during symptoms	H1/H2 blockers, mast cell stabilizers
Seronegative APS	Miscarriages, headaches, memory loss, balance difficulty, fatigue, cognitive dysfunction, livedo reticularis, arterial or venous thrombotic events	Same as seropositive APS, but with negative laboratory tests	Anti-cardiolipin antibodies, beta 2 glycoprotein antibodies	Aspirin, clopidogrel, warfarin, heparin
<p>POTS, postural orthostatic tachycardia syndrome; TTT, tilt table test; OH, orthostatic hypotension; BP, blood pressure; HR, heart rate; NCS, neurocardiogenic syncope; LOC, loss of consciousness; SFN, small fiber neuropathy; ENFD, epidermal nerve fiber density; SGNFD, sweat gland nerve fiber density; QSART, quantitative sudomotor axon reflex test; TST, thermoregulatory sweat test; UCTD, undifferentiated connective tissue disease; ANA, anti-nuclear antibodies; RF, rheumatoid factor; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; NSAIDs, non-steroidal anti-inflammatory drugs; ASIA syndrome, autoimmune/inflammatory syndrome induced by adjuvants; HLA, human leukocyte antigen; PTLDS, post-treatment Lyme disease syndrome; hEDS, hypermobility Ehlers-Danlos Syndrome; MCAS, mast cell activation syndrome; PGD-2, prostaglandin 2; H1/H2, histamine 1/histamine 2; APS, antiphospholipid syndrome.</p>				

Prognosis of CDAF appears to be chronic and variable, given that misdiagnosis and delay in diagnosis are common [2]. Additionally, prognosis of each disorder has not been well studied in the scientific literature, considering that the etiology is multifactorial and response to therapy is diverse, since many patients have medication sensitivities and allergies and are generally prone to medication adverse effects. Psychotherapy, cognitive-behavioral therapy, physical therapy, and occupational therapy can be beneficial in improving the functional status and reducing the suffering of patients with CDAF. However, there is generally limited access, resources, and local infrastructure that is available to patients with CDAF to utilize these therapies. Thus, much like pharmacotherapy, nonpharmacologic treatment options for CDAF have not been well studied, are typically fragmented, expensive, and are not always covered by the patients' health insurance plans.

Pharmacotherapy

Pharmacotherapy for CDAF is diverse and consists of medications from various classes (Table 1) [3–11]. At the onset of CDAF, antidepressants and anti-anxiety medications are often prescribed, given that a misdiagnosis with major depression, generalized anxiety disorder, or panic disorder is common in this patient population. When these medications fail to result in improvement or cause significant side effects that are quite prevalent in patients with CDAF, medications for headache, neuropathic pain, muscle tension, gastrointestinal symptoms and sleep disturbance are often prescribed. Once patients are referred to specialists, a more tailored pharmacotherapy can be employed. For example, in patients with Postural Orthostatic Tachycardia Syndrome, medications that reduce heart rate (e.g., beta blockers), enhance vasoconstriction (midodrine), or expand plasma volume (fludrocortisone) are used. In Mast Cell Activation Syndrome, antihistamines (e.g., loratadine and ranitidine) are commonly employed, and in Undifferentiated Connective Tissue Disease, anti-inflammatory medications (ibuprofen, celecoxib), immunomodulating therapy (hydroxychloroquine, intravenous immunoglobulin), and steroids are utilized to treat joint pain and fatigue. A more tailored treatment approach is typically more efficacious than the general approach to CFS or fibromyalgia and may result in significant improvement in the patient's symptoms, quality of life, and functional status.

Paradigm Shift

With that in mind, a clinical paradigm shift is necessary in patient care to view CDAF entities and its relationship to CFS and fibromyalgia. Ultimately, a change in paradigm would lead to a change in algorithm in how patients with chronic fatigue are evaluated, diagnosed, and treated. Rather than uniformly apply the diagnosis of CFS or fibromyalgia to any patient with chronic fatigue or chronic pain, it is more effective to stratify the patients into more specific diagnoses in the CDAF group. The obvious benefit is that a more specific diagnosis yields better treatment options than what is usually employed in patients with CFS or fibromyalgia. The benefit does not only come from more specific treatment options; it also comes from the prospects of better health insurance coverage under different diagnostic codes as well as a possibility to participate in clinical trials available for a specific disorder.

Future Direction

Over the last few decades, an alarming rise in the number of patients presenting with chronic pain or chronic fatigue has been observed in clinical practice [16, 17]. In addition to markers of genetic predisposition, research into the etiology of CDAF may need to include the impact of the environmental factors, such as atmospheric pollutants, food preservatives, hormonal disruptors, agricultural pesticides, pharmaceutical excipients, and possible vaccine adjuvants, as potential activators of the immune system. Since autoimmunity and immune-mediated etiology is presumed to be the basis for most of the subgroups of CDAF and likely for CFS in general, future research should focus on identifying targeted therapies, specifically immunomodulatory and biological therapy for CDAF and CFS. Currently, small therapeutic trials of rituximab and immunoadsorption demonstrated efficacy in patients with CFS [13–15], suggesting that a more robust therapy than simply symptomatic management is a distinct possibility in the future treatment of patients with CFS.

The role of the rheumatologists, immunologists, neurologists, and pain management specialists is critical in the evaluation, diagnosis, and management of CDAF and its subsets. Rather than apply a broad umbrella term of CFS or fibromyalgia to a diverse patient population with chronic fatigue or chronic pain, clinicians should attempt to stratify the patients into one of the disorders of CDAF. When every disorder in the CDAF group is ruled out, then

the default diagnosis can be CFS and/or fibromyalgia. This approach may lead to a change in case definition and prevalence of CFS and fibromyalgia, and would also result in improved diagnosis and treatment of patients with chronic and disabling disorders associated with fatigue.

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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