

Relationships among rhinitis, fibromyalgia, and chronic fatigue

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ABSTRACT

New information about the pathophysiology of idiopathic nonallergic rhinopathy indicates a high prevalence in chronic fatigue syndrome (CFS). This article shows the relevance of CFS and allied disorders to allergy practice. CFS has significant overlap with systemic hyperalgesia (fibromyalgia), autonomic dysfunction (irritable bowel syndrome and migraine headaches), sensory hypersensitivity (dyspnea; congestion; rhinorrhea; and appreciation of visceral nociception in the esophagus, gastrointestinal tract, bladder, and other organs), and central nervous system maladaptations (central sensitization) recorded by functional magnetic resonance imaging (fMRI). Neurological dysfunction may account for the overlap of CFS with idiopathic nonallergic rhinopathy. Scientific advances in fMRI, nociceptive sensor expression, and, potentially, infection with xenotropic murine leukemia-related virus provide additional insights to novel pathophysiological mechanisms of the "functional" complaints of these patients that are mistakenly interpreted as allergic syndromes. As allergists, we must accept the clinical challenges posed by these complex patients and provide proper diagnoses, assurance, and optimum care even though current treatment algorithms are lacking.

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The differential diagnosis of nonallergic rhinitis (NAR), where IgE and TH2 lymphocyte mechanisms are absent, is broad.¹ Exclusion of syndromes associated with atopy, inflammation, anatomic disorders, endocrinopathies, and other identifiable causes leaves idiopathic nonallergic, noninfectious, rhinopathy with no clear etiology.² The phenotypes, prevalences, and, potentially, even pathophysiology of NAR may differ in different regions of the world.

We propose that the NAR of chronic fatigue syndrome (CFS)³ and fibromyalgia⁴ accounts for a major proportion of idiopathic NAR (iNAR). CFS shares many characteristics with chronic multisymptom illness,⁵ Gulf War illness,⁶ dysautonomic rhinopathy,⁷ fibromyalgia,⁸ multiple chemical sensitivity, and somatoform disorder (Fig. 1).⁹ This contention can be

more readily appreciated by comparing the impact and factors associated with iNAR and CFS.

The burden of NAR is significant. In one 4-year cohort of 1,726,084 patients, 29% had one or more medical visit for rhinitis. NAR was diagnosed in 21% of these rhinitis patients. When compared with allergic rhinitis (AR) subjects, those with NAR were significantly more likely to have sinus radiology; nasal surgery; receive diagnoses of sinusitis, otitis media, sleep apnea, and fatigue; and to receive medications for non-respiratory conditions ($p < 0.001$).¹⁰ The proportion of subjects with nonallergic complaints who had CFS, dysautonomic rhinopathy, and multiple visits (and charges) for their other concomitant disorders remains to be determined.

NONALLERGIC MECHANISMS

Nonallergic mechanisms may cause nasal complaints in about one-quarter of all adolescents and adults with rhinitis.¹¹ Women have twice the prevalence as men. In general, subjects with NAR have symptoms that are as severe but more persistent than AR subjects. Headaches (odds ratio in favor of NAR, 1.94; 1.12–3.37; $p = 0.019$), including periods of midfacial pain that may be interpreted as sinusitis, were more frequent in NAR. However, sneezing and itchy eyes within specific allergy seasons, beneficial effects of antihistamines, concomitant bronchial hyperresponsiveness, asthma, and food allergy were more indicative of an atopic etiology (odds ratio in favor of NAR, <0.40 , with $p < 0.009$).

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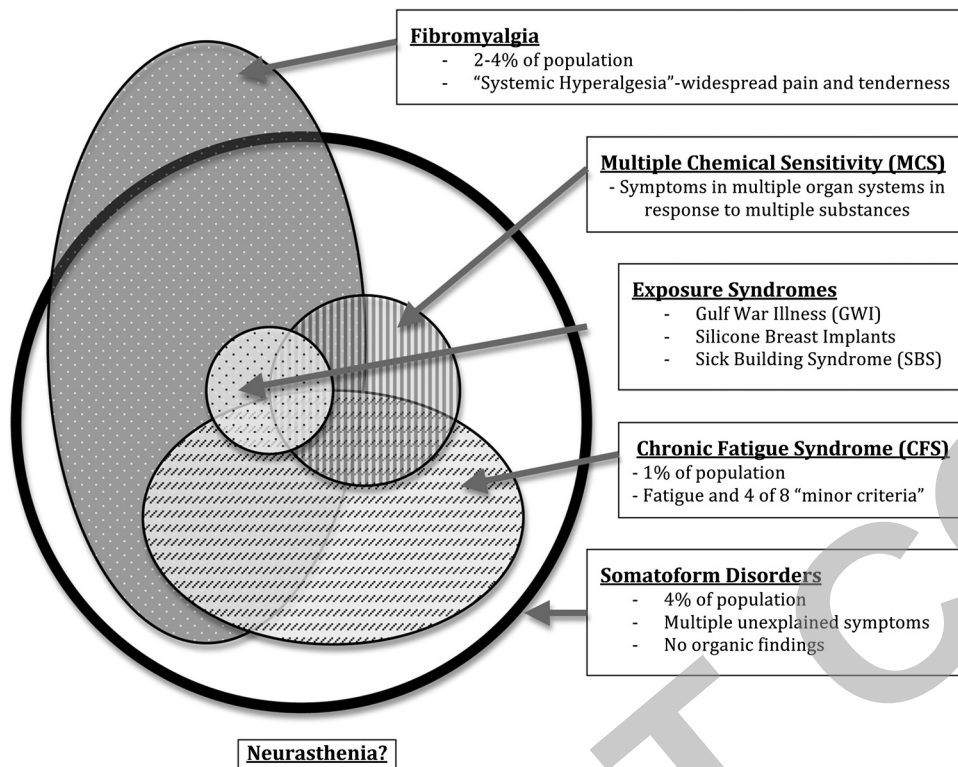


Figure 1. Overlap of chronic fatigue syndrome, fibromyalgia, and other disorders. (Used with permission of the copyright holder JN Baraniuk.)

Comparable data are not specifically available for CFS and iNAR.

Inflammatory cells and epithelial shedding were not present in NAR.¹² There were no changes in nasal expression of human α -defensins 1 to 3, β -defensins 1 to 4, or Toll-like receptors 2 and 4 compared with nonrhinitis control samples.¹³ The absence of inflammation is consistent with the absence of any benefits of topical nasal corticosteroids in the rhinitis of CFS subjects.¹⁴ Steroids were effective for AR and nonallergic turbinate hypertrophy, suggesting that these pathologies did not have elevated prevalences in CFS and iNAR.¹⁵ Terfenadine was also ineffective.¹⁶

Inhalation of cold dry air leads to some degree of rhinorrhea in virtually everyone. This stimulus may involve nasal mast cell activation and sensory nerve stimulation that generate nasal symptoms and recruit parasympathetic cholinergic reflexes. These reflexes lead to glandular secretion that is readily blocked using anticholinergic agents.¹⁷ In contrast, nonallergic rhinopathy subjects respond to cold dry air provocation with characteristic nasal airflow obstruction.¹⁸ Some evidence suggests that individuals with nasal cold air sensitivity may have reduced ability to compensate for the evaporative water losses that occur during exposure to cold air.¹⁹ The water losses are likely to lead to hyperosmolarity of the nasal epithelial lining fluid. If so, the responders may have analogous reactions to those of CFS subjects.¹⁹

Cholinergic reflexes have been proposed to have important anti-inflammatory functions.²⁰ Vagal stimulation down-regulates levels of tumor necrosis factor, interleukin (IL) 1, IL-6, and IL-8. However, there is no effect on IL-10 or transforming growth factor β . Vagotomy increases the severity of ileus, colitis, and pancreatitis in animal models. The α 7-nicotinic acetylcholine receptor may be responsible for the anti-inflammatory effects of vagal nerve stimulation because receptor agonists reduce the severity of these inflammatory states and counter the effects of vagotomy. Similar results occur in knockout mice lacking the α 7-nicotinic acetylcholine receptor. The presence of mRNA for nicotinic acetylcholine receptor subunits has been assessed by reverse-transcriptase polymerase chain reactions (RT-PCR) in full thickness mucosal biopsy specimens from 6 normal and 18 severe sinusitis and nasal polyposis subjects.²¹ The α 3- and α 7-subunits were detected in 100% of normal and 89 and 62% of diseased subjects, respectively. mRNA for α 4 and β 2 were detected in 44–83% of the two groups. Only β 4-subunits showed a significant difference between healthy (50%) and diseased (6%) subjects ($p = 0.035$). There is no information on the distribution of these nicotinic receptor subunits on postganglionic sphenopalatine neurons or nasal mucosal resident and inflammatory cells in healthy, allergic, nonallergic, and idiopathic rhinopathy subjects. The relevance of these findings to the muscarinic cholinergic end organ effects in the nose is not clear.

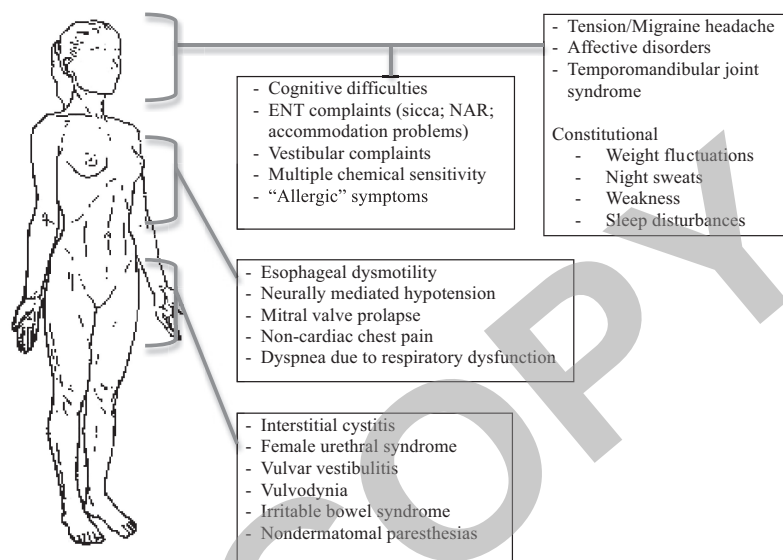


Figure 2. Syndromes associated with chronic fatigue syndrome and fibromyalgia. (Used with permission of the copyright holder JN Baraniuk.)

Epithelial nerve growth factor ($p = 0.03$) and sub-epithelial innervation (PGP9.5, $p = 0.01$) were higher in NAR and AR than nonrhinitic tissue. Immunoreactivity for the Nav1.7, Nav1.8, and Nav1.9 neural sodium ion channels that are involved in nociception were significantly elevated in AR and NAR.²² This raises the potential that sensory neuropathy may contribute to iNAR and CFS. Dysfunctional spinal cord and other central mechanisms contribute to peripheral neuropathies²³ and the systemic hyperalgesia of fibromyalgia and CFS. We propose that nonallergic, neurological rhinitis represents a chronic regional pain syndrome (CRPS III; reflex sympathetic dystrophy). Nociceptive hypersensitivity appears to be present in iNAR. iNAR and CFS subjects may represent a "sentinel" population who can detect suboptimal indoor air quality.²⁴ They likely react to nonallergenic components of inhaled air such as fine particulate material, products of fermentation (e.g., fungal products), and other volatile organic compounds. AR may coexist and account for the so-called "mixed rhinitis."

Patients with iNAR have significant autonomic abnormalities involving sudomotor, cardiovagal, and, occasionally, adrenergic dysfunction.²⁵ Their highest symptom scores were 3.9 of 5 for rhinorrhea (95% CI, 3.1–3.9), 3.6 (95% CI, 2.8–3.3) for nasal obstruction, and 3.2 (95% CI, 2.4–3.3) for headache.⁷ The rhinorrhea tended to be watery (71%) rather than mucoid (29%). The sensation of simultaneous bilateral air-flow obstruction was present in one-half, with unilateral in 29%. Migraine headaches were found in 51%. Significant otolaryngological symptoms included lightheadedness (67%) without vertigo (17%). Visceral syndromes included irritable bowel syndrome (88%), palpitations (72%), and gastroesopha-

geal reflux in 62% (Fig. 2). Hypervagal and mixed vagal and adrenergic imbalance were detected by tilt table testing, Valsalva maneuver, hyperventilation, and isometric hand grip responses. Heart rate variability in iNAR has also been attributed to a hyperactive parasympathetic nervous system.²⁶ These complaints, syndromes, and autonomic alterations are comparable with those identified in CFS.

CFS AND RELATED DISORDERS

CFS is defined by having severe, sudden onset fatigue lasting at least 6 months that leads to significant disability with a decrement in work productivity and strain on the ability to perform activities of daily living (Table 1).^{27–29} No other medical or psychiatric condition may be present to explain the fatigue. This excludes most chronic illnesses such as thyroid, diabetes, other endocrinopathies, cerebrovascular, cancer, autoimmune, and other inflammatory conditions. In addition to severe fatigue, there must be new onset of ancillary symptoms lasting for at least 6 months. At least four of the following eight symptoms must be present: sore throat, sore lymph nodes, sore muscles (myalgia), sore joints without swelling or redness (arthralgia), new-onset headaches, neurocognitive disability with difficulty concentrating and perceived short-term memory loss ("brain fog"), sleep disturbances, and exertional exhaustion. The latter is one of the stronger ancillary predictors. It is readily identified in subjects who perform exercise of any type that is more than their usual daily exertion, who then develop a relapse in their condition with extreme exhaustion that may send them to their bed for several days with severe fatigue, pain (the first five minor

Table 1 Center for Disease Control and Prevention chronic fatigue syndrome (CFS) criteria

Clinicians should consider a diagnosis of CFS if these two criteria are met:

1. Unexplained, persistent fatigue that is not caused by ongoing exertion, is not substantially relieved by rest, is of new onset (not lifelong), and results in a significant reduction in previous levels of activity
2. Four or more of the following symptoms are present for ≥ 6 mo:
Impaired memory or concentration
Postexertional malaise (extreme, prolonged exhaustion, and sickness after physical or mental activity)
Unrefreshing sleep
Muscle pain
Multijoint pain without swelling or redness
Headaches of a new type or severity
Sore throat that is frequent or recurring
Tender cervical or axillary lymph nodes

Source: Ref. 29.

criteria), and disordered neurocognitive function. These criteria were first selected by consensus after statistical review of a large number of cases, and have subsequently been validated in epidemiological studies.³⁰

Multiple chemical sensitivity is often present. This is a chronic, acquired disorder with widespread complaints that are associated with subthreshold or subtoxic exposures to a wide variety of unrelated chemicals and other exposures. Idiopathic environmental intolerance is another acquired syndrome with multiple recurrent symptoms brought on by diverse conditions of inhaled air that are well tolerated by the majority of others. Sick building syndrome occurs in subjects who develop acute healthy and discomfort effects that are temporally linked to time spent in the specific location.³¹ Building-related illness refers to symptoms of diagnosable illness that can be identified and attributed directly to airborne building contaminants. Symptoms may be traced to fungal infestations and inhalation of products of fermentation. Each of these sensitivity syndromes require that psychiatric and psychological illness be critically assessed and found to not contribute to the symptomatology.

Associated disorders include fibromyalgia (Table 2)³²; posttraumatic fatigue syndrome,³³ postchemotherapy fatigue syndrome; irritable bowel; irritable bladder; irritable vagina (vulvodynia),³⁴ adverse events after immunization syndrome that often leads to chronic fatigue, arthralgia and myalgia³⁵; and

Table 2 American College of Rheumatology 1990 criteria for fibromyalgia

For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied; widespread pain must have been present for at least 3 mo; the presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia:

1. History of widespread pain.

Definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation.

Definition. Pain, on digital palpation, must be present in at least 11 of the following 18 sites:
Occiput: Bilateral, at the suboccipital muscle insertions

Low cervical: Bilateral, at the anterior aspects of the intertransverse spaces at C5–7

Trapezius: Bilateral, at the midpoint of the upper border

Supraspinatus: Bilateral, at origins, above the scapula spine near the medial border

Second rib: Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces

Lateral epicondyle: Bilateral, 2 cm distal to the epicondyles

Gluteal: Bilateral, in upper outer quadrants of buttocks in anterior fold of muscle

Greater trochanter: Bilateral, posterior to the trochanteric prominence

Knee: Bilateral, at the medial fat pad proximal to the joint line

Digital palpation should be performed with an approximate force of 4 kg.

For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender is not to be considered "painful."

Source: Ref. 32.

other nonspecific “functional” disorders that may involve neural dysregulation and localized or systemic hyperalgesia.³⁶ The American College of Rheumatology case designation criteria for fibromyalgia rely on pain and tenderness.³⁷ The symptom of pain must be present continuously for at least 3 months and affect all four quadrants of the body. This means left and right sides above and below the waist plus the axial skeleton. The axial skeletal pain can involve the neck, thoracic and lower spine, ribs (costochondritis), and sternum. The sign of hyperalgesia, or tenderness, is pain elicited by pressure. The standard research criteria is to induce pain by pressing with one’s thumbs over “tender points” (formerly trigger points) until the thumb nail blanches (~4 kg of pressure).³⁸ The subject must complain of pain at ≥ 11 of 18 traditional, standardized tender points. These are located bilaterally at the occiput, cervical spine, supraspinatus, trapezius, anterior ribs, lateral epicondyle, gluteus maximus, greater trochanter, and medial knee. This type of hyperalgesia assessment may be misleading, because administration of deep pressure using the thumb of the investigator causes pain that the subject can not control. As a result, anxious subjects have a higher number of positive tender points compared with healthy control subjects. Once one painful point has been pushed, the patient has a higher probability of anxiously preparing for more pain and is more likely to complain of a painful response.³⁹ Pressure at the patient’s thumb nail may be sufficient to identify those with lower deep pressure-induced hyperalgesia.

Our clinical investigations suggest about two-thirds of CFS subjects meet fibromyalgia criteria.⁴⁰ The majority complained of “sinus” problems. CFS subjects had higher rhinitis scores⁴¹ and about one-half had positive skin tests. This was comparable with a nonselected healthy control population. Despite the positive skin tests, most of the CFS subjects did not have typical symptoms of histamine-induced itch, sneeze, watery rhinorrhea, or eosinophilia. Therefore, AR and atopy were unlikely to explain their diverse spectrum of complaints. Instead, a pattern emerged of nasal sensitivity to irritant substances leading to sensations of congestion $\pm$ rhinorrhea. CFS subjects had more facial tenderness than healthy control or acute sinusitis subjects.⁴² Their fatigue was associated with “functional” syndromes of irritable bowel, irritable bladder, and other mucosal disorders.

CFS and control subjects were compared for a wide range of complaints and psychometric parameters (Table 3). CFS had significantly more physical symptoms, fatigue, pain, depression, anxiety, anger, physical dysfunction, and poor quality of life.^{43–46} The ability of irritants to stimulate sensations of nasal

Table 3 Treatment of chronic fatigue syndrome and related disorders

Confirm diagnosis and affirm this to patient
Encourage adaptive, flexible attitude
Aerobic exercise
Lifestyle accommodations for QOL
Cognitive behavioral therapy
Support internal locus of control
Hydration: i.v. saline or Gatorade
Sleep: trazadone
Muscle relaxation: cyclobenzaprine
Anxiety: clonazepam
Atypical depression: TCA, SSRI May reduce neurogenic inflammation
Atypical migraine headaches
Identification and avoidance of nasal irritants:
Weather changes, humidity
FDA definition of NAR
Cigarette smoke
Cleaning products
Gasoline
Products of fermentation (e.g., fungi and bacteria)
Nasal saline p.r.n.
Nasal Vaseline or other gel p.r.n.
Nasal menthol in low doses (not eucalyptus)
Activates “cool” TRPM8 receptors
Nasal anticholinergic spray if excessive stimulus-induced congestion and rhinorrhea
Terfenadine and topical fluticasone propionate were ineffective in properly powered RDBPC studies

FDA = Food and Drug Administration; NAR = nonallergic rhinitis; QOL = quality of life; RDBPC = randomized, double-blind, placebo controlled; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant; TRPM8 = transient receptor potential melanostatin 8.

congestion and discharge⁴⁷ and sensitivity to tobacco smoke⁴⁸ were generally increased in CFS but were not present in all of the CFS subjects. About one-half had multiple chemical sensitivity. Anxiety has already been shown to be significantly greater in women with either allergic or iNAR compared with control subjects.⁴⁹ CFS/FM subjects had greater hyperalgesia, higher prevalence of interstitial cystitis and irritable bladder symptoms,⁵⁰ dyspnea, and airway complaints.^{40–42}

PROPOSED MECHANISMS OF CFS AND iNAR

Atopy has been proposed as a cause of CFS because rates of allergy skin tests of 50% were deemed significantly higher than generally assumed rates of 20–30% extrapolated from the previous decade.⁵¹ CFS subjects complained of skin rashes, urticaria, rhinitis, asthma, and drug and food sensitivities. These conditions were

designated as "atopic" even though there were no confirmatory or provocation testing to evaluate IgE-mediated mechanisms. It was concluded that 83–90% of CFS subjects were "atopic." Subsequent work has found equal levels of IgE and allergy skin tests in CFS and control populations.⁵² As early as 1992, Metzger's group had proposed that NAR was the most likely diagnosis.⁴ Their finding was largely ignored as investigators stampeded to the TH2 dysfunction hypothesis of CFS pathology. Lymphocyte stimulation test results showing IL-6 and IL-8 release in response to endotoxin and other stimuli in CFS specimens fueled these studies. However, nasal lavage fluid levels of eosinophil cationic protein, neutrophil elastase, nerve growth factor, tumor necrosis factor α , and IL-8 were not different in CFS from nonrhinitis controls but were lower than in acute eosinophilic sinusitis.⁵³

Theories of Epstein-Barr, cytomegalovirus, herpes types 6 and 8, various mycoplasma, and other infections abound,⁵⁴ but are poorly supported by data. The original cardinal features of CFS (myalgia, sore throat, fatigue, and sensation of fever) resembled an infectious illness, and were described as epidemics. However, careful epidemiological evaluations showed a uniform rate of CFS of ~2% when multiple communities with and without "epidemics" were evaluated. Many studies relied on high viral antibody titers as evidence for infection. However, higher Epstein-Barr virus titers and immune dysfunction have been reported in subjects living under high stress conditions such as the caregivers to Alzheimer patients.⁵⁵ This led to the theory that chronic physiological stressors may have modulated immune responses leading to CFS.

Dysautonomia provides a more plausible explanation for the pathophysiology in CFS and FM. Impaired sympathetic response to stressors such as exercise, muscle contraction, noise, tilt table tests, and other stimuli may be linked to elevated parasympathetic influences⁵⁶ and contribute to postural hypotension, irritable bowel syndrome, migraine headaches, and NAR (as noted previously). Theories of neurological dysfunction including hypothalamic and other central deficits provide a stronger basis for understanding this overlapping spectrum of illnesses. These theories are now supported by functional magnetic resonance imaging, positron emission spectroscopy, and other advanced methods to evaluate visceral nociceptive alterations in the insula, executive and decision-making dysfunction in the anterior cingulate gyrus, and inappropriate linkage of fearful memories, other emotions, and avoidance behaviors through the amygdala and other limbic system centers.⁸

Dysfunctional nasal mucosal and nociceptive nerve axon responses have been implicated in the rhinitis of CFS.⁷ Unilateral hypertonic saline nasal provocations were found to stimulate unilateral sen-

sations of pain, nasal congestion, and rhinorrhea that were significantly higher in CFS, active AR, and acute sinusitis subjects compared with nonrhinitis controls. Secretion of serous and mucous materials from submucosal glands increased in dose-dependent fashion in control subjects. However, CFS subjects did not show the same dose dependence and, instead, had level or plateaued secretion rates. These findings add another dimension of altered axon response-mediated mucosal secretion production in the rhinitis of CFS.

CENTRAL SENSITIZATION IN CFS AND RELATED ILLNESSES

"Central sensitization" invokes the concept that chronic, repetitive, pain-inducing ("nociceptive") peripheral stimuli can cause molecular changes in neuronal neurotransmitters, receptors, and regulatory signaling pathways ("neuronal plasticity").^{57–59} These changes may occur at multiple levels simultaneously. Peripheral nociceptive nerve endings may respond to neurotrophins to express higher levels of acid sensing ion channel 3, transient receptor potential vanilloid 1 (capsaicin receptor), and purinergic receptor (P2Y₄ and P2Y₄) that allow a smaller stimulus to cause neuron depolarization ("peripheral sensitization"). Strangely, mRNA for these same nociceptive proteins are expressed in peripheral blood cells, and are significantly up-regulated 24 hours after exhausting exercise in CFS subjects but not healthy controls.⁶⁰ This postexercise quantitative RT-PCR test may become a viable diagnostic test for CFS if it can be confirmed and validated in additional subjects.

Similar changes can alter the synaptic activity between the central ending of primary sensory and nociceptive neurons with secondary, ascending sensory neurons in the superficial dorsal horn ("spinal sensitization"). Augmented transmission of painful afferent messages to the central nervous system increases perceptions of that painful stimulus. This is hyperalgesia ("increased pain"). Fibromyalgia involves diffuse pain, and has been considered "systemic hyperalgesia." Dysfunctional regulatory interneurons and aberrant function of other neurotransmitter systems (*e.g.*, endocannabinoids) can facilitate inappropriate activation of ascending pain neurons by large-diameter light touch and proprioceptive neurons to generate allodynia ("parallel pain"). One component of this dysfunctional system is thought to be reduced descending, antinociceptive, aminergic (norepinephrine, serotonin, and dopamine) inhibitory neural signaling from the dorsal pons, periaqueductal gray matter, and median Raphe nuclei. Supratentorial changes can lead to increased receptivity at central somatosensory locations such as the insula and parietal cortices. This pattern of

molecular and anatomic events lead to an increase in permissive afferent painful signaling combined with decreased protective, descending pain-preventative “efferent” signaling. The net effect is a decrease in the threshold required to activate perceptions of pain and other forms of discomfort.

Functional magnetic resonance imaging studies have shown evidence for reduced pain thresholds and excessive cognitive dysfunction in CFS, fibromyalgia, and other syndromes.^{61–64} These molecular and synaptic mechanisms of neural plasticity may be involved in the transition from occasional migraines to chronic, severe daily headaches, peripheral nerve damage to CRPSs (CRPS I and II, formerly known as reflex sympathetic dystrophy), phantom limb pain, occasional myalgia into fibromyalgia, tiredness into chronic fatigue syndrome, and beneficial fear into debilitating posttraumatic stress disorder.⁶⁵ We postulate that the discomfort, “congestion,” “sinus headaches,” and other sensory experiences of idiopathic rhinopathy and the rhinitis of CFS are the consequences of these neurological processes and may represent a CRPS of the trigeminal and associated sensory nerves and their central connections. These concepts demand a fresh diagnostic and therapeutic approach to CFS, NAR, and other allied syndromes if we are to do no harm and help our patients with these complaints.

TREATMENT OF CFS AND iNAR

Because CFS, fibromyalgia, and associated disorders have been controversial entities, drug and other therapeutic algorithms have been difficult to establish.⁵⁵ There are no specific drugs for CFS. Instead, many older medications have been adapted to treat the central and peripheral nervous system manifestations. One problem for the absence of clear guidelines is the lack of rigorous clinical trials. Reid *et al.* identified 45 systematic reviews, randomized clinical trials, and observational studies that could be evaluated for their quality of evidence.⁶⁶ Cognitive behavioral therapy and graded exercise programs were beneficial. Antidepressants as a group, oral glucocorticoids, and mineralocorticoids did not show uniform effectiveness. Therapies with unknown or unlikely effectiveness included dietary supplements, evening primrose oil, homeopathy, intramuscular magnesium, oral nicotinamide adenine dinucleotide, and galantamine. Allergy shots without clear indications of atopy were unlikely to be beneficial. Prolonged rest was potentially harmful.

The foundation of a successful CFS patient–doctor relationship is for the doctor to understand the widespread nature of CFS-related symptoms. Onset of the full-blown syndrome may be sudden and follow a

prolonged and presumably viral, flu-like illness, or a period of immobilization after an illness, motor vehicle accident, surgery, or other period of relative inactivity. About one-half of normal subjects, and especially those who exercise on a very regular basis, develop irritability, myalgia, and some affective changes when put on bed rest. Other CFS subjects may have a slower onset with different symptoms appearing, waxing and waning over decades. Isolated fatigue without the other minor criteria defines idiopathic fatigue. Fatigue may also be associated with major affective disorder, endocrinopathies, and cachexia associated with cancer and inflammatory diseases. In the strictest definition, CFS can not occur in the presence of any other illness associated with fatigue. This is in contrast to the systemic hyperalgesia and anxiety of fibromyalgia, because this diagnosis is often made in subjects with autoimmune and other illnesses. This type of inconsistency between definitions only adds to the confusion about this family of disorders.

CFS patients have often had extremely negative experiences with the medical establishment. “It’s all in your head,” is a common refrain that denigrates and infuriates the patient, and indicates a lack of empathy, knowledge, and ethics by the treating physician. A modern twist is that “It’s all in your head,” is a reasonable summary of the locus of neurological dysfunction within the central nervous system. Therefore, the foundation of treatment is to establish an honest exchange with the subject. Often, they will appear with a suitcase of laboratory and other tests. These can be reviewed and negative complete blood counts, thyroid-stimulating hormone, sedimentation rate, C-reactive protein, antinuclear antibody, and rheumatoid factor results confirmed. If the symptoms make you consider performing the fifth or sixth intensive imaging study, then it is time to take a step back and review the symptoms for the presence of fatigue, diffuse pain, intermittent and relapsing cognitive difficulties that are often described as a “brain fog,” and especially the finding of exertional exhaustion. Activity to an extent greater than usual daily exertion is likely to lead to extreme fatigue and pain that exile the CFS subject to their bed for several days.

Recognition that the subject has CFS and affirming their diagnosis may be one of the most reassuring statements that the physician can provide these subjects. The patient’s attitude must be gauged, and their strengths used to build the therapeutic relationship. The time to diagnosis is often long; this means the time to understanding, adaptation, and symptomatic control will generally be prolonged. Cognitive behavioral therapy and yoga can be valuable for teaching patience, self-control, and self-reliance. The

relationship can be fragile and benefits from regularly scheduled appointments and treatment plans that include patient involvement such as keeping diaries to evaluate symptoms and effects of physiotherapy, massage, and other kinesthetic treatments. Support groups are especially valuable to provide insights to patients that doctors may not be aware of.

Pharmacotherapy should be carefully tailored to symptoms. The sense of fatigue and generalized pain often responds to cyclobenzaprine. It is important to start at the lowest doses of 2.5 or 5 mg at night, to increase at the slow rate of 5 mg/month, and to clearly educate the CFS patient that it may take 6 months or more to notice improvements. If morning grogginess or other symptoms occur, the dose should be reduced to the last well-tolerated dose. Trazadone, again starting with lower doses such as 50 or 75 mg and increasing as needed, can be valuable as a nonaddictive sedative. Some patients benefit from the substitution of low doses of imipramine or other tricyclic drugs. Selective serotonin reuptake inhibitors, and potentially those that also block norepinephrine uptake may be useful in some cases. Acetaminophen is generally advised for pain. It is important to avoid the temptation to turn to opiate drugs because of the risks of addiction. Referral to a pain specialist should be considered for severe pain. Hypothalamic dysfunction is common, and so central hypothyroidism should be addressed by thyroid hormone supplementation. Recently introduced drugs for neurogenic pain such as pregabalin (Cymbalta) have not been systematically studied in CFS. Their effects appear to have been significant in fibromyalgia subjects with relatively mild and short-term pain. Magnesium as an oral supplement or weekly intramuscular injections may reduce pain sensations.

The NAR of CFS has been frustrating to treat. The aforementioned medications do not appear to modify this rhinitis. A simple approach is to use nasal saline lavage, menthol gels, and other emollients. Gustatory, cold air, and other forms of cholinergic, dysautonomic rhinitis with excessive glandular secretion respond to anticholinergic sprays. Terfenadine and topical glucocorticoids were ineffective in clinical trials. Effects of topical antihistamines have not been studied. Topical capsaicin has been shown to reduce the sensation of nasal congestion for >6 months. However, high doses of capsaicin along with a decongestant and local anesthetic are required for safe administration. Future treatments may include capsaicin receptor antagonist drugs (transient receptor potential vanilloid 1 blocking agents); sodium, calcium, and potassium ion channel modulators; and drugs that interfere with central glutaminergic activity at any of its various receptors.

XENOTROPIC MURINE LEUKEMIA VIRUS RELATED VIRUS (XMRV) And CFS

XMRV has recently been associated with CFS.⁶⁷ XMRV is a γ -retrovirus that has been studied for >30 years and has not previously been linked to human illness. The new findings indicate that 67% of CFS, but only 3% of healthy control subjects, have the single-stranded viral RNA in their blood cells when amplified by nested RT-PCR. Leukocytes were shown to harbor the proteins (Western blotting) and to shed virions by electron microscopy. Infection of a permissive prostate cell line was possible *in vitro*. It is difficult to assess if these findings translate into the potential for transmission between individuals. A possible mechanism for spreading the virus is currently only a topic for speculation, because no cases have been established. The case designation in this series of subjects also needs to be examined to determine if this group is representative of CFS seen around the globe or is a subtype or mimic of CFS. Indeed, each part of this relationship must be intensively investigated and validated before XMRV is considered the "CFS virus".

XMRV has also been detected in an advanced form of human prostatic cancer. It is not known if this represents a chance occurrence, a virus that by happenstance can "invade" these metastatic neoplastic cells, or a causative agent. The need for additional scientific findings is clear from other studies that have shown no association of XMRV and cancer in humans.^{68,69}

CONCLUSION

It is highly unfortunate that the attitudes of physicians toward CFS, fibromyalgia, iNAR, and functional disorders such as irritable bowel syndrome are so highly stigmatized and negative.⁷⁰ Physicians tend to stereotype this group as having certain undesirable traits including transgression of social roles by failing to conform to the work ethic and instead adopting a role of "sickness." This stereotyping may be related to the physician's training and need to make a physical diagnosis for an illness with no precise anatomic localization. This can lead to conflict between the doctor and patient over causes and management. These factors strain the therapeutic relationship and can lead to outright rejection of the complexly demanding CFS/fibromyalgia/iNAR/irritable bowel syndrome/"brain fog" patient by the managing practitioner. The physicians generally did not consider referral for mental health interventions because they were not familiar with the therapies or deemed them unavailable or unnecessary. This occurred despite the recognition of the critical roles of social and psychological factors in these patients' well being. Sadly, doctors' beliefs

served as barriers to patient treatment. Negative stereotyping of patients the absence of awareness about the best currently available medical evidence regarding CFS and NAR translated into ignorance and lack of confidence in current management strategies. These barriers are a formidable challenge in dealing with these syndromes that are “all in the head.” It leads one to wonder who’s head is having the problem. This is exemplified by recent reports of exercise-induced up-regulation of nociceptive sensor ion channels and a potential association of a subgroup of CFS with XMRV that may suddenly turn this wayward diagnosis into mainstream medicine. This supracervical focus does have a silver lining because this is the anatomic location of the upper airways and most of the body’s neurons that are dysfunctional in CFS and iNAR. Widespread dispersal of newer evidence of proteomic, functional magnetic resonance, and other brain imaging studies, and, hopefully the introduction of novel, effective drugs, will serve to overcome these medical biases and improve the lot of this misunderstood group of patients and their enigmatic disorders.

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