

Alphabet Soup

CFS research is complicated by myriad overlapping conditions that have both symptoms and diagnostic criteria in common. This not only impacts research, it makes it hard to diagnose and treat these illnesses.

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FM

Every patient with chronic fatigue syndrome knows about overlapping conditions. FM. IBS. MCS. TMD. There's a veritable alphabet soup of symptoms and disorders that seem to overlap in CFS patients. This not only complicates research, it makes diagnosis and management of these illnesses harder for physicians. It also complicates life for patients, who must deal with skepticism from the physicians, family members and friends who find it hard to believe that someone with so many ailments isn't a hypochondriac, depressed or eager to assume the sick role to get attention. The struggle to find health care professionals who are knowledgeable about these overlapping illnesses is an added burden for patients.

In fact, research suggests that it may be rare for a CFS patient not to have concurrent symptoms of other illnesses, and some patients actually receive formal diagnoses for multiple conditions. Many

Hypermobility syndrome, which is characterized by unusually flexible joints, should be investigated as an overlapping condition or predisposing factor for CFS. In treating and studying CFS patients since 1987, I have been struck by the presence of joint hypermobility in almost every one.

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experts believe that the diagnosis given to a patient with one of these illnesses may depend more on the patient's main symptom and the specialty of the treating physician than on the actual illness process. For instance, a patient can go to a rheumatologist and receive a diagnosis of fibromyalgia, but go to an internist and be diagnosed with CFS.

This doesn't mean, however, that these are all the same illness masquerading under different names. Overlapping or unexplained clinical conditions share symptoms such as fatigue and pain; disability out of proportion to physical examination findings; no diagnostic test or biomarker to confirm laboratory abnormalities; and an apparent association with stress. Although clinicians have described these illnesses for decades, unraveling the links between them has been problematic. Inadequate information exists on the cause, mechanisms, natural history, prognosis and medical management for these conditions.

Could these overlapping illnesses share the same pathophysiology, which manifests differently in various subsets of patients? Or do different triggers result in illnesses with similar symptomology? Could inadequate case definitions and diagnostic criteria be responsible for some of the overlap?

We don't know the answers to all these questions yet. Nevertheless, researchers understand much more about overlapping conditions than we did two decades ago.

Overlapping definitions

A 1999 review in the *Lancet* compared the case definitions of 12 unexplained clinical conditions for which published criteria exist, including CFS, fibromyalgia (FM), irritable bowel syndrome (IBS), multiple chemical sensitivity (MCS), temporomandibular joint disorder (TMD), tension and migraine headache, chronic low-back pain, interstitial cystitis (IC), chronic pelvic pain, chronic nonbacterial prostatitis and postconcussion syndrome. Substantial overlap in symptoms occurred in the case definitions. For example, bloating or abdominal distention was noted in 8 of the 12 definitions; headache in 8; and

MCS

fatigue and abdominal pain in 6 each. Nonetheless, some syndromes, such as CFS and FM, frequently co-occur despite different symptom criteria. This means similarities in formal case definitions are unlikely to account for all, or even most, of the overlap among syndromes.

A related issue that has been rarely examined is whether distinct symptoms are present in each unexplained clinical condition. In the absence of diagnostic markers, such unique symptoms could help clinicians identify patients with unexplained clinical conditions. Researchers have reported that painful lymph glands and fever distinguished CFS from FM, and constant instead of episodic pain distinguished FM from TMD. Other investigators found that five pelvic and bladder symptoms occurred more frequently among patients with interstitial cystitis than FM, whereas three symptoms—muscle pain, inability to concentrate and balance problems—were more commonly reported in FM.

In our work on overlapping conditions at the University of Washington, unique features of CFS were subjective fever and sore throat. Special features of FM were low-back pain that improved with heat or massage and worsened with sitting or standing. TMD patients were best distinguished by facial pain in the jaw muscles or joints. Nevertheless, even these distinguishing symptoms were experienced so frequently by all the patients with unexplained conditions that they were nondiagnostic.

Overlapping symptoms & syndromes

Many studies have been conducted, and comparisons of patient groups demonstrate high rates of overlap across all the conditions examined. For example, it has been estimated that in referral clinics up to 70% of FM patients meet the case definition for CFS, and 35-70% of those with CFS have FM. Studies investigating the relationship between FM and TMD have demonstrated that 13-18% of temporomandibular joint disorder patients meet criteria for fibromyalgia compared to 2% of the general population. Conversely, 75% of FM patients satisfy the published case definition for TMD compared to 15% of the general population. Other chronically painful syndromes such as tension headache and low-back pain also commonly occur in CFS and FM.

TMD

Gulf War Vets Have 16 Times Greater Risk for CFS

According to an article published in the *Annals of Internal Medicine* in June 2005, veterans of the 1991 Gulf War are 16 times more likely to have developed CFS than nondeployed veterans. The study offers some of the most convincing evidence to date that Gulf War deployment may have led to chronic fatigue syndrome in a significant number of veterans.

Gulf War syndrome is often considered an overlapping condition with CFS, but the link between the two is unclear. The study authors note, "The mechanisms by which deployment increased the risk for chronic fatigue syndrome in Gulf War veterans are still unknown."

Twelve different conditions were measured, but only CFS, fibromyalgia, dermatologic conditions and dyspepsia were more prevalent among the deployed vets. CFS was the only illness associated with dramatically increased risk for Gulf War vets.

This cross-sectional study, conducted 10 years after the war, was large, including 1,061 deployed veterans and 1,128 controls. It was sponsored by the U.S. Department of Veterans Affairs.

Likewise, irritable bowel syndrome occurs in 58-92% of CFS patients, 32-80% of FM patients and 64% of TMD patients. Lifetime rates of strictly defined IBS among patients with CFS, FM and TMD greatly exceed the frequency in control subjects (64-92% vs. 18%) and the general population (9-21%). Clinical similarities have also been shown in the symptoms reported by FM and IC patients. With regard to multiple chemical sensitivity, 53-67% of CFS patients report a worsening of their illness with exposure to various chemicals, and 55% of FM patients experience symptoms consistent with MCS. On the other hand, 30% of patients with MCS experience CFS.

IC

Objective findings

Most studies haven't examined objective findings in unexplained clinical conditions. In those that have, such findings fall into two categories: physical examination and physiological abnormalities. Tender points are the most commonly shared physical examination finding among overlapping conditions. Several studies have shown that the average number of tender points was higher in TMD and IC patients than in control groups, but lower than in FM patients. A few investigations have also evaluated sleep and laboratory markers.

Other investigations on similarities between unexplained clinical conditions have focused on mechanisms related to pain perception. The most

ASPECTS OF THE ILLNESS

frequent and consistent objective finding among the unexplained clinical conditions investigated has been a decrease in pain threshold and tolerance. However, the mechanisms underlying these changes in pain perception remain unresolved.

Proposed explanations

Researchers have proposed several reasons to explain the similarities between these unexplained clinical conditions: the illnesses may share the same pathophysiology; localized symptoms may result from a single, more generalized underlying condition; or they may be illnesses on a continuous spectrum. Sleep, diet, exercise or other factors likely mediate the nature and extent of symptom expression and may determine which syndrome is manifested. Litigation, stress, medication side effects and maltreatment in the medical system may also influence the symptom pattern and course.

Several mechanisms for individual unexplained

Attributing unexplained clinical conditions solely to psychological distress or psychiatric explanations is no longer widely accepted. However, many patients with unexplained clinical conditions report an illness onset in conjunction with acute or chronic physical or emotional events. Both physical and emotional stress can perturb the function of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic system, resulting in sensitization of the central nervous system by neuropeptides, ultimately altering the processing of pain signals. Although intriguing, the applicability of this theory to all overlapping conditions requires further testing because key differences in the HPA axis have been reported between CFS and FM. Likewise, mediators of growth hormone function differ in these two disorders, and likely across other overlapping conditions.

Proponents of the second mechanism believe that the symptoms of unexplained clinical conditions can be attributed to chronic pain and changes in pain threshold and perception. For example, in a study of postconcussion syndrome, cognitive and neurobehavioral complaints were not considered unique to the illness, but rather a feature of chronic pain. Pain threshold studies and tolerance testing—and a general lack of structural and functional abnormalities in muscle tissue—suggest the pain in unexplained clinical conditions results from central processing deficits rather than peripheral abnormalities. A defect in pain control mediated by serotonin, leading to hypersensitivity, has been proposed for fibromyalgia and headache. Localized injury might also sensitize the central nervous system to incoming pain signals, leading to decreased pain thresholds at other body sites. In this regard, the relatively high number of tender points outside of the jaw in temporomandibular disorder is consistent with a more global pain sensitivity disorder.

Lastly, it seems highly probable that overlap among unexplained clinical conditions is due, in part, to the complex interplay between genes and the environment. Research studies suggest that there is a genetic predisposition that puts family members of CFS and FM patients at greater risk for developing these illnesses.

At the present time, the evidence is weak for a simple, discrete unifying mechanism. A major limitation is that none of the proposed mechanisms can account for the occurrence of overlapping clinical

IBS

40% of CFS Patients May Have MCS

Multiple chemical sensitivity, first described in 1952, has since engendered over 20 names including environmental illness and, most recently, idiopathic environment intolerance (IEI). The syndrome is characterized by multiple symptoms triggered by low-level chemical exposure. Common symptoms include fatigue, difficulty concentrating, depressed mood, memory loss, weakness, dizziness, headaches, heat intolerance and arthralgias. CFS studies have shown that as many as 40.6% of CFS sufferers also meet the criteria for MCS/IEI (Jason, Taylor, Kennedy, 2000).

There are several theories as to the cause including allergy, toxic effects and neurobiological sensitization but etiology has not yet been confirmed. The absence of scientific agreement about MCS/IEI has generated controversy among clinicians, patients, researchers and regulatory agencies. Although it has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association and several other medical organizations, it has achieved levels of credibility in workers compensation claims, tort liability and the EPA.

In its advice for dealing with MCS/IEI, the American Academy of Family Physicians has urged sensitivity, stating that clinicians must care responsibly and compassionately for patients experiencing this difficult syndrome.

clinical conditions have also been proposed. Three mechanisms are most often implicated in the spectrum of unexplained clinical conditions:

- 1) physiologic processes, especially neuroendocrine abnormalities, autonomic nervous system dysfunction and low perfusion of brain structures;
- 2) pain perception and the effects of chronic pain;
- and 3) genetic vulnerability.

CFS

conditions in a large proportion of affected individuals. The best model for mechanisms that could account for unexplained clinical conditions may be one in which environmental, cultural, psychosocial, biological and genetic factors are all necessary, but individually insufficient for illness to occur.

Future directions

Studies of unexplained clinical conditions often suffer from methodological shortcomings that question the conclusions drawn and limit comparability across studies. More rigorous methodology is needed to assure reliable findings.

Given the extent of the overlap, a first step for future studies is the inclusion of the symptoms or diagnostic criteria for other conditions likely to co-exist with CFS. This will be especially important in treatment trials since people with multiple syndromes may be more difficult to treat than those with a single condition. While the available studies indicate that defects in central nervous system processing of pain signals are present in individual unexplained clinical conditions, more work is needed to elucidate mechanisms. We would argue that comparative study designs of physiology underlying the changes in pain perception (e.g., neurotransmitters, brain blood flow levels) may provide the most convincing evidence.

Lastly, consideration of the relative influences of genetic and noninherited factors also could help reveal the underlying relationships between overlapping conditions. Research should also investigate the onset of the first condition relative to the appearance of other clinically unexplained disorders.

As a final caveat, describing an illness as unexplained should not be taken to mean unexplainable or imaginary. Researchers and clinicians involved with patients suffering from unexplained clinical conditions would do well to remember Osler's words that the study of medicine "begins with the patient, continues with the patient and ends . . . with the patient." ■

Recent Fibromyalgia Findings

Although there are some immunological aberrations in FM, including a decreased number of natural killer cells, most researchers now believe that the illness is not an immune system disorder. Essentially, there is nothing specifically immunological in fibromyalgia and if there is, whatever little there is, I think it is secondary to the central nervous system problem that fibromyalgia patients have, says Dr. Muhammad Yunus. It's a chronic, neurologic disease.

Numerous research studies have found biologic abnormalities in FM patients and it's increasingly uncommon to hear physicians suggest the illness is all in your head. There was a time when we thought fibromyalgia was psychosomatic. We now understand the pain in fibromyalgia is caused by an abnormality in the central nervous system in which pain sensations are amplified, explains Dr. Robert Bennett, an FM expert at Oregon Health Sciences University.

This central sensitization theory is described in detail in the August 2005 issue of the *Journal of Rheumatology*. Basically, the theory is that fibromyalgia results from miscommunication among nerve impulses in the central nervous system the brain and spinal cord causing FM patients to feel intense pain when they should only feel mild discomfort or fatigue.

Recent investigations found multiple triggers for this amped-up response to pain. For instance, FM patients have three to four times higher levels than normal of substance P, a central nervous system neurotransmitter involved in pain processing. Researchers also found lower levels of substances that diminish pain sensation, such as serotonin, norepinephrine and dopamine.

Dr. Daniel Clauw, director of the Center for the Advancement of Clinical Research at the University of Michigan, says, "The pain of fibromyalgia is not occurring because of some injury or inflammation of the muscles or joints. There is something wrong with the way the central nervous system is processing pain from the peripheral tissues. It's overamplifying the pain."

Pharmaceutical companies are now interested in developing drug treatments based on the new research.

IBS and CFS Overlap

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders diagnosed in the United States. It's characterized by abdominal pain and associated with alterations in bowel patterns such as cramping, bloating, diarrhea and constipation. Symptoms often contribute to absences from school or work, reduced productivity and diminished quality of life.

As with CFS, IBS occurs most often in women. For IBS, the prevalence is approximately 2 to 2.5 times greater in women than men. Women with IBS are more likely to report disorders including migraine headaches, bladder discomfort and chronic pelvic pain some of which are also common to CFS. There also appears to be higher incidence of interstitial cystitis among women with IBS, as among women with CFS.

In 2000 the direct and indirect costs of diagnosis and symptom management of IBS were estimated at \$1.66 billion. A 2004 study established the validity of the Work Productivity and Activity Impairment questionnaire (WPAI) as a tool for measuring relative severity of IBS, with quantifiable productivity loss and impairment seen at most levels of the illness.