Overactive CNS Processing Tied to Fibromyalgia

When viewed together, neuroimaging studies show strong neurobiologic underpinnings of disorder.

BY CHRISTINE KILGORE
Contributing Writer

An "overwhelming" amount of data now suggest that patients with fibromyalgia and a number of overlapping pain syndromes have augmented pain or sensory processing in the central nervous system, resulting in real differences in pain tolerance, judging from the findings of a recent review.

Genetic findings also are accumulating that suggest specific gene mutations may predispose individuals to developing fibromyalgia (FM), according to the authors.

"It is time for us to move past the rhetoric about whether these conditions are real, and take these patients seriously as we endeavor to learn more about the causes and most effective treatments for these disorders," reported Dr. Daniel J. Clauw, professor of rheumatology at the University of Michigan, Ann Arbor, and director of the U-M Chronic Pain and Fatigue Research Center, and Richard E. Harris, Ph.D., a researcher at the center and the university.

The hyperactivity of pain processing mechanisms that characterizes FM and related conditions—from irritable bowel syndrome to tension headache and temporomandibular syndrome—can occur in association with psychological factors, "but psychological factors are not in any way required for an individual to develop or maintain this augmented central pain state," they wrote.

Other investigators said in an interview that they hope to see more reviews like it, particularly since many studies of FM are low budget, small and too easily dismissed unless they are viewed together.

Neuroimaging studies, for instance, "are providing a consistent picture" when viewed together of strong neurobiologic underpinnings for FM, said Dr. Nancy Klimas, professor of medicine at the University of Miami. "But if you pull them apart, you can find faults with any one study in it having limited power, or some other limitation."

"This is what [the authors] are saying—'look at the whole picture, it's impressive,' " said Dr. Klimas. "There's some real science to go behind the pain observation."

Dr. Klimas said the review reminded her of a grand-rounds lecture she heard several years ago, in which a "prominent" department chair told students and faculty that fibromyalgia "is all in patients' heads."

"He essentially said, don't let these patients talk to each other, don't let them read anything, don't let them have any support group meetings," Dr. Klimas said. "I was livid. These patients [with FM] are often treated badly by their physicians. It's bad enough leaving without any hope that something can be done, but it's worse leaving a doctor's office having been made to feel small or patronized."

Dr. Laurence Bradley, professor of medicine in the division of clinical immunology and rheumatology at the University of Alabama, agreed that the literature is ripe for strong conclusions. "The [review authors] are correct. A lot of new findings have emerged in the last 5-8 years … regarding gene variance that's associated with FM itself or with [related] disorders.

"And a lot of the neuroimaging work that has been done has demonstrated very convincingly that people with FM have enhanced or abnormal transmission of sensory signals through the CNS," he said. "Behavioral studies—laboratory pain studies—also show consistent displays of abnormal pain responses in individuals with FM."

In their review, Dr. Clauw and Dr. Harris described functional imaging studies done with single-photon emission computer tomography (SPECT) and functional magnetic resonance imaging (fMRI) that show differences in neural activation between patients with FM and pain-free controls. The studies indicate that FM patients have abnormalities within their central brain structures, they said.

There is evidence in FM that an "increased gain" in pain processing is driven by defects in both descending inhibitory pathways for pain processing and in spinal excitatory activity, the authors added.

Biochemical studies have supported the notion that the pathology might be a result of high levels of pronociceptive compounds (such as "substance P"), low levels of antinociceptive compounds, or both. Conversely "there is considerable evidence that this increased gain could occur because of a deficiency in one of the major endogenous analgesic pathways, the descending antinociceptive serotonergic-noradrenergic pathway" (Curr. Pain Headache Rep. 2006:10;403-7).

The "ultimate proof" that defective central control mechanisms are playing a role in FM and overlapping pain conditions comes from randomized clinical trials showing that neuroactive compounds that either increase inhibitory activity (such as serotonin-norepinephrine reuptake inhibitors) or decrease facilitatory activity (such as antiepileptics) can be efficacious in treating FM as well as neuropathic pain, said Dr. Clauw and Dr. Harris.

Dr. Bradley said that one of the "missing pieces of information" in the growing knowledge of pain transmission in FM is its original source.

"Where's the starting point?" he asked. "[Many experts] think it originates from abnormalities in the deep muscle tissue, but at this point we have a much better understanding of what goes on at the spinal level than we do of what factors contribute to the initiation of sensory signals."

What's missing from the review itself, he and others noted, is the "consistent" evidence of altered neuroendocrine function in patients with FM.

Dr. Robert Bennett, who has led studies in this area, said that FM also appears to be a manifestation of an abnormal acute stress response involving abnormalities in levels of cortisol and growth hormone, an imbalance in sympathetic and vagal tone, and other phenomena—a notion that puts FM at least partly in the same camp, for underlying mechanisms, as chronic fatigue syndrome.

"The major things we know now [about FM] relate to the pain system," said Dr. Bennett, professor of medicine at Oregon Health and Science University, Portland. "The neuroendocrine abnormalities—the manifestations of the acute stress response—have still, I think, been underinvestigated."

Dr. Klimas, director of the University of Miami's chronic fatigue syndrome research center, said that more than 60% of her patients with the syndrome meet the case definition of FM as well, which reflects at least in part the fact that the FM definition is looser and more inclusive while the chronic fatigue syndrome definition has many exclusionary criteria.

Dr. Bradley added that a number of recent studies have also shown a familial aggregation of pain sensitivity. The studies show that first-degree relatives of patients with FM tend to have the "same sorts of unusual sensitivities to pain and abnormal pain responses," even though this isn't always manifested as FM. ■

Fibromyalgia and Collisions Often Unrelated, Study Suggests

BY JEFF EVANS
Senior Writer

WASHINGTON — An association between a motor vehicle collision and the development of widespread body pain in some individuals was not supported by findings from an ongoing prospective study comparing two different cohorts.

However, the study of more than 8,000 people did suggest that such collisions may be associated with a post-crash onset of axial skeleton pain, John McBeth, Ph.D., reported at the annual meeting of the American College of Rheumatology.

"Physical stressors have been implicated in the onset of widespread pain disorders; particularly, whiplash experienced during a motor vehicle collision has been associated with the etiology of fibromyalgia," said Dr. McBeth, senior lecturer in rheumatic disease epidemiology at the University of Manchester (England).

In the current study, a cohort of 1,499 patients aged 17-70 years who were involved in a motor vehicle collision (MVC) were compared with a control cohort of 6,792 individuals aged 25-65 years who participated in a pain survey.

Among patients who did not have widespread pain at baseline, 641 of 951 MVC patients and 3,058 of 3,780 control subjects participated in a 15-month follow-up. The rate of new-onset widespread pain in these subjects was similar between the MVC (8.4%) and control groups (11.6%). There also was no relationship between the severity of the collision and the development of widespread pain. These comparisons were adjusted for age, gender, pain at baseline, and psychological status. "This surprised us because we expected to see some kind of relationship between crash severity and the onset of widespread pain," he said.

New-onset axial skeleton pain occurred at similar rates in the MVC (20%) and control cohorts (21%). But patients who had a severe collision were significantly more likely to report new-onset axial skeleton pain at the 15-month follow-up than were control patients.

This relationship persisted after adjustment for pain and psychological status at baseline.

The patients who developed axial skeleton pain may be "on the path" to developing widespread pain. With longer follow-up, the rate of new-onset widespread pain may be higher, Dr. McBeth said.

Previous studies have found that physical and psychosocial stressors are associated with an increased risk of new-onset widespread pain.

In one study of people who were in MVCs, the rate of new-onset fibromyalgia after the accident was significantly greater among those patients who had a cervical spine injury than it was in those patients who had leg fractures (Arthritis Rheum. 1997;40:446-52).

A case-control study found about 40% of fibromyalgia patients could recall a stressful event that may have precipitated the onset of their symptoms; these patients were most likely to report that a fracture, surgery, or workplace injury preceded the symptoms. Fibromyalgia patients were not more likely than controls to recall an MVC as a precipitating factor (Rheumatology [Oxford] 2002;41:450-3).

But an abstract presented at the annual meeting of the ACR in 2004 reported that among patients who had presented to an emergency department, the rate of new-onset fibromyalgia was significantly higher in those who had been in an MVC than in a control group of patients who had had a minor laceration. The MVC patients who reported neck pain at the time of presentation had the highest risk for developing fibromyalgia.

However, those studies did not take the role of psychological factors into account in relation to the onset of widespread body pain, Dr. McBeth said.

When he and his colleagues conducted a population-based, prospective study of 1,658 adults who did not have widespread pain at baseline, they found that individuals who reported high levels of somatic symptoms, illness behavior, psychological distress, and fatigue at baseline had a significantly increased risk of developing chronic widespread pain after 1 year (Arthritis Rheum. 2001;44:940-6). ■

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