Fibromyalgia Pain Linked to Brain Dysfunction

BY DIANA MAHONEY

DESTIN, FLA. — Structural, functional, and chemical changes that were observed in the brains of fibromyalgia patients suggest that the clinical symptoms of the chronic pain syndrome may have a neurologic basis, M. Catherine Bushnell, Ph.D., said at the Congress of Clinical Rheumatology.

"Fibromyalgia is very different from other rheumatologic diseases, probably because it isn't a rheumatologic disease," said Dr. Bushnell, director of the Alan Edwards Centre for Research on Pain at McGill University in Montreal.

Although the diagnosis of fibromyalgia continues to be based on the subjective report of widespread pain and sensitivity to palpation, the identification in recent years of various psychophysical and neurophysiologic alterations in fibromyalgia patients provides evidence that altered CNS physiology may underlie fibromyalgia symptoms, she said.

In addition to the characteristic joint and muscle pains that bring fibromyalgia patients to the rheumatology clinic, multiple studies have shown that these patients are hypersensitive in many ways, Dr. Bushnell said. "In one study, we used heat stimuli on the arms of fibromyalgia and control patients, and compared their reactions over a period of 20 seconds. The fibromyalgia patients graded it as a significantly more intense pain stimulus" than did the healthy controls, she said, noting that similar results were seen in separate studies in which patients and controls rated their response to an injection of hypertonic saline solution into the anterior tibialis muscle and in assessments of auditory and olfactory sensitivity.

Although fibromyalgia patients appear to have altered thresholds to pain, they have normal responses to innocuous sensations. "The threshold for fibromyalgia patients' detection of warmth and cold is not different" than that of healthy controls, said Dr. Bushnell. "But when you ask them to indicate when it becomes painfully hot or painfully cold, they will say it's painful at a lower temperature or higher temperature."

These findings suggest that "an endogenous pain modulatory system in the brain is not working," Dr. Bushnell said, "which is what more and more researchers who study this think about fibromyalgia: that it is not only a problem of the brain, but specifically that it is a problem of the normal modulatory system."

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Hallmark changes in brain anatomy have also been linked to fibromyalgia. "The most commonly observed change is a decrease in brain gray matter relative to healthy controls," Dr. Bushnell said. One 2007 study comparing total brain gray matter volume in 10 fibromyalgia patients and 10 healthy controls showed that the fibromyalgia patients had a more than threefold greater age-associated decrease (J. Neurosci. 2007;27:4004-7).

"The longer the disease duration, the greater the gray matter loss," Dr. Bushnell noted. "Each year of fibromyalgia was equivalent to approximately 9.5 times the gray matter loss seen in normal aging." Analyses of regional gray matter density showed that the regions of gray matter loss were those associated with pain modulation or stress, including the cingulate, insular, and medial frontal cortices, parahippocampal gyri, and thalamus.

The observed gray matter changes are not unique to fibromyalgia patients. "In fact, similar changes have been observed in the brains of other patients with chronic pain syndromes, including chronic tension-type headaches and irritable bowel syndrome," said Dr. Bushnell. "This suggests that the pathology in the brain in fibromyalgia patients is linked to their experience of pain."

Changes in white matter tracts of fibromyalgia patients have also been observed. A recent German study in which investigators used a combination of magnetic resonance diffusion-tensor imaging (MR-DTI) and MR imaging of voxel-based morphometry (MR-VBM) demonstrated microstructural and volume changes in the central neuronal networks involved in the sensory-discriminative and affective-motivational characteristics of pain, anxiety, memory, and regulation of the stress response, Dr. Bushnell said. According to the study investigators, the results revealed that the organization of cerebral microstructures is more complex and active in the areas of the brain involved in pain processing, emotion, and the stress response (Arthritis Rheum. 2008;58:3960-9).

In addition to anatomical abnormalities, studies of brain neurochemistry in fibromyalgia patients have linked changes in this domain to patients' experience of pain, Dr. Bushnell said. In a study designed to evaluate the release of dopamine (which has a role in pain modulation) in response to muscle pain among fibromyalgia patients, she and her colleagues used PET to examine the binding potential of a specific dopamine receptor in the brains of fibromyalgia and healthy controls during an injection of a painful hypertonic saline and nonpainful normal saline. The control subjects released dopamine in the basal ganglia during the painful stimulation, whereas the fibromyalgia patients did not. The amount of dopamine release correlated with the amount of perceived pain in the healthy controls only, indicating that fibromyalgia patients have an abnormal dopamine response to pain (Eur. J. Neurosci. 2007;25:3576-82).

More recently, researchers have demonstrated disruptions in the mu-opioid binding potential in brain regions that are known to play a role in pain modulation (J. Neurosci. 2007;27:10,000-6), as well as correlations between the clinical features of fibromyalgia and hippocampal metabolite abnormalities (J. Pain 2009;10:47-52) and between dopamine metabolism and changes in gray-matter density (J. Pain 2009;10:609-18).

The brain changes in fibromyalgia may have an impact on the emotional and cognitive status of fibromyalgia patients. "Fibromyalgia patients routinely complain of what they call 'fibrofog.' They can't think straight, they can't remember things, and in fact studies have shown deficits on various cognitive performance tests, particularly in working-memory capacity, long-term memory, and verbal fluency," Dr. Bushnell said. "When our data came out showing the changes in gray matter in fibromyalgia, I started getting e-mails from patients saying, 'That makes sense. I now know why I'm feeling this way.' We don't know yet if there is a relationship there, but it's something we're studying."

Additionally, she noted, "there has been one small study so far showing a correlation between some of the anatomical changes in the brain and cognitive deficits, which suggests that it's possible that some of these neurological and chemical changes in the brain may underlie these various symptoms" (Brain 2008;131:3222-31).

Based on the research to date, "we know that fibromyalgia patients have altered pain processing, loss of brain gray matter, changes in white matter tracts, changes in neurochemical function, and cognitive deficits," Dr. Bushnell said. Despite all of the brain alterations, however, it's still not clear whether fibromyalgia is a primary disorder of the brain.

"It might be a consequence of early life stress or prolonged or severe stress, which in turn affects brain function and structure in some people," she said. "More data are accumulating from chronic pain studies suggesting that the longer the pain goes on, the more anatomical changes you see in the brain, indicating that the brain changes may be related to the duration of pain, so it is probably very important that treatment begins as early as possible."

Dr. Bushnell has served as a consultant for and received research support from several pharmaceutical companies and is a member of the speakers bureau for Eli Lilly & Co. ■

Migraine May Be Risk Factor for Cervical Artery Dissection

BY MICHELE G. SULLIVAN

PHILADELPHIA — Migraine with aura seems to be a risk factor for cervical artery dissection, Dr. Ville Artto concluded in a poster presented at the International Headache Congress.

His study of 626 subjects found that migraine and migraine with aura were significantly more common among both men and women who had experienced a cervical artery dissection than among control subjects.

The pathophysiologic link between migraine and cervical artery dissection remains unclear, Dr. Artto said. More than 60% of the patients who had active migraines at the time of their dissections, however, reported that their migraines were alleviated after the incident.

Patients with migraine and cervical artery dissection may represent a link between ischemic stroke and migraine, wrote Dr. Artto of the Helsinki (Finland) University Central Hospital. "This connection may represent common pathophysiological or genetic background, or both," he wrote.

The study included 313 patients, mean age 46 years, with cervical artery dissection and 313 age-matched controls. Cases were significantly more likely to smoke than were controls (37% vs. 23%), and female cases were significantly more likely than female controls to be using oral contraceptives (36% vs. 25%).

Migraine was present in 36% of cases and in 23% of controls. Migraine with aura was present in 23% of cases and 12% of controls. Both differences were significant. In women, migraine was present in 54% of cases and 35% of controls; migraine with aura was present in 35% of cases and 18% of controls. Among men, migraine was present in 27% of cases and 16% of controls; migraine with aura was present in 16% of cases and 0.4% of controls.

When the investigators compared the characteristics of the dissection between patients with and without migraines, they found similar rates of vertebrobasilar dissection, bilateral dissection, occlusion, and intracranial dissection. The National Institutes of Health Stroke Scale score was not different at onset (3 in migraineurs and 4 in nonmigraineurs). The Rankin score was similar at 3 months (1 in both groups). The rate of ischemic stoke was 68% in migraineurs and 73% in nonmigraineurs, which was not a significant difference.

The International Headache Society and the American Headache Society sponsored the congress. Dr. Artto did not report any relevant conflicts of interest. ■