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Expert Opinion

Migraine and Fibromyalgia

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Migraine is frequently associated with fibromyalgia syndrome (FM), which may have a common pathophysiologic basis.

CLINICAL HISTORY

This 45-year-old woman has a 17-year history of migraine without aura occurring about 20 days monthly which have gradually increased over the years from about twice a month initially without medication overuse. She also has about a 10-year history of diffuse pain with 12/18 tender points on examination. Other symptoms include chronic insomnia, depression, chronic fatigue, irritable bowel syndrome, and short-term memory problems for several years. The neurological examination was normal. Blood tests for auto-immune and thyroid disease, vitamin B12 levels, and an MRI scan of the brain have been normal.

Questions: Is FM more prevalent in migraineurs? What about for other primary headache types? What is FM? What might be the underlying pathophysiology for both disorders? Should headache specialists and neurologists diagnose and treat patients with FM or refer them to primary care specialists and rheumatologists? Are there treatments which might benefit both disorders?

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EXPERT OPINION

Migraine and Other Primary Headaches and Fibromyalgia Syndrome.—This is a case of comorbidity between chronic migraine and FM. FM is 6 times more common in women while migraine is 3 times more common. The prevalence of this disorder in the community increases with age from 2% at age 20 to as high as 8% at age 70; most patients present between the ages of 30 and 55. FM can be a disabling disorder of largely unknown cause although there is a growing body of evidence to support the mechanism of a central sensitization mechanism underlying chronic musculoskeletal pain in these patients.[1] Despite the frequent association between FM and primary headaches, rheumatologists classified it as "an unexplained clinical condition."[2]

FM is more common among migraineurs than in the general population. In a study of 101 consecutive patients with transformed migraine seen in Brazil, FM was present in 35.6%.[3] Migraineurs with FM were more likely to have insomnia, older age, and more incapacitating headaches than those without. Insomnia and depression predicted FM in patients with transformed migraine. In a

Conflict of Interest: None

series of 92 consecutive migraineurs seen in an Israeli headache clinic, 22.2% of the female patients and none of the male patients were diagnosed as suffering from FM.[4] In a retrospective chart review of 223 consecutive migraineurs (84% female) attending a headache clinic in Ohio, 23% had FM (95% female) and a high prevalence of depression and anxiety.[5] In a cohort of 144 consecutive migraineurs referred to our tertiary center in Italy, the prevalence of FM was 16.8%.[6] A Danish study of 46,418 twins found FM in 1.2% of those with migraine vs 3% of those without migraine and with a higher percentage in all female patients, more so those with migraine with aura (2.8% vs 6% in those without migraine).[7] The self-administered survey questionnaire probably underdiagnosed the number of participants with migraine.

In our cohort of 217 consecutive headache patients, 36.4% of the patients were found to have FM.[6] FM was most common among chronic migraine and chronic tension-type headache patients. Headache, frequency of headache, pericranial muscle tenderness, anxiety, and sleep inadequacy were especially associated with FM comorbidity. Tension-type headache was the most common primary headache associated with FM, with a 59.01% prevalence, compared with episodic and chronic migraine, with 28.8%. There was no difference between chronic tension-type headache and chronic migraine for FM syndrome prevalence that suggests that FM is a syndrome complicating these 2 types of chronic headache. Allodynia was present in 74.3% of migraineurs. A common pathophysiologic basis has been hypothesized for FM and tension-type headache with central sensitization of nociceptive pathways.[8] We had too few cases of other primary chronic headaches in our series to explore whether FM is more prevalent in other types.

Headache is common among patients with FM. In a study of 100 patients with FM, recurring headache occurred in 76% with the following types: migraine, 48% (without aura, 27%, with aura, 21%); tension-type, 18%; migraine and tension-type, 16%; and analgesic overuse, 8%.[9] Headache predated the onset of FM on average 7 years before the onset of FM symptoms. Similarly, in a study of 33 FM patients, current migraine was present in 45% and a lifetime history of migraine in 55%.[10]

FM: Pathophysiological Basis for Migraine Comorbidity.—According to the American College of Rheumatology, FM is a chronic pain syndrome of unknown etiology characterized by diffuse pain over more than 3 months and tenderness in at least 11 tender point sites out of 18.[11] Despite these apparently simple diagnostic criteria, the syndrome appears more complex with associated symptoms including nonrestorative sleep, fatigue, and cognitive dysfunction.[12] There is a growing body of evidence that abnormal pain processing at a central level has a role in FM pathogenesis.[1] In FM, there is no evidence for peripheral sensitization as the cause of hyperalgesia, given the absence of real tissue damage. Peripheral sensitization almost always depends on local inflammation which may lead to decreased nociceptive thresholds.

Despite extensive investigations, no tissue pathology, structural abnormalities, or evidence for a source of chronic stimulation of pain afferents has been detected in FM patients while clear phenomena of temporal summation of pain (or windup) and central sensitization have been extensively reported.[1] Neurophysiologic methods able to explore the nociceptive afferent system suggest that FM patients resemble a model of severe central nonorganic ("sine materia") pain,[13] where weak painful stimuli, delivered at both tender and not tender points, are able to induce cortical hyperactivation for a phenomenon of generalized hyperalgesia.[14]

These phenomena are confirmed by functional magnetic resonance imaging findings of significantly greater activation in the anterior insula and the cingulate cortex in response to painful stimuli.[15] A similar model of cortical hyperactivation under experimentally induced painful stimuli were observed in the course of migraine attacks, chronic migraine and chronic tension-type headache,[16] suggesting that in these syndromes, central sensitization, which is a well-recognized phenomenon complicating both migraine and tension-type headache,[17,18] may be facilitated by the abnormal function of cortical areas devoted to the cognitive and affective expression of pain. This may be the

reason why FM more commonly occurs in chronic headache patients.

Studies have reported that FM patients display a generalized "hypervigilance" to multimodal inputs that was associated with specific "hyperattention" to painful stimuli which was specially manifest during stimulation of tender points.[19,20] A study investigating the intensity-dependence of auditory-evoked cortical potentials showed that FM patients were hypervigilant to acoustic stimuli and showed reduced inhibition of the response to noxious and intense auditory stimuli, a phenomenon which the authors attributed to serotonergic deficit.[21] The pattern of "cortical hypervigilance" to multimodal stimuli is well known in migraine patients[22] as well as in FM patients.

Recently, we aimed to increase our knowledge about central sensitization mechanisms in FM, exploring habituation to repetitive painful stimuli, delivered at both tender and not tender points.[23] Thompson and Spencer[24] have defined habituation as a decrement in the amplitude of the response of the sensory cortex to repeated presentations of similar stimuli (in the absence of receptor or effector fatigue) to avoid brain overstimulation. In nonneuropathic pain syndromes, such as migraine and cardiac X syndrome, reduced habituation to repetitive, painful stimuli suggested an abnormal level of activation and excitability in cortical areas, which exacerbates the perceived intensity of painful stimuli.[25,26] We ascertained that FM shares with migraine a pattern of reduced habituation of cortical areas devoted to perception and elaboration of painful stimuli.[23] In the same study, we found that this pattern of reduced habituation of nociceptive cortex to repetitive painful stimuli was more expressed in FM patients with higher self-reported levels of depression, which is a factor aggravating chronic pain.[23]

Clinical Management of FM and Common Causes of Comorbidity.—FM shares with migraine and probably with other causes of comorbidity[2] a biobehavioral model of generalized multimodal cortical hypervigilance with reduced habituation to pain, sustained by altered neuronal excitability, and aggravated by depression. In this view, the use of antidepressants and antiepileptic drugs, which specifically demonstrated an inhibitory action on the phenomenon of reduced habituation in migraine patients,[27] is largely supported. Antidepressants such as amitriptyline and venlafaxine, which may be effective for FM,[28,29] may also be effective for migraine and tension-type headache prevention. Similarly, gabapentin may be effective for FM[30] and prevention of migraine.

The occurrence of musculoskeletal pain, as the first symptom of FM, justifies its clinical management by rheumatologists, although the functional abnormalities of neuronal circuits elaborating multimodal stimuli and specifically pain require more attention by neurologists by individualized therapeutic approaches. Further, the frequent occurrence of FM comorbidity as an aggravating factor of chronic headaches suggests the opportunity for headache specialists to evaluate the occurrence of these syndromes, which may compromise the effect of therapies on quality of life and global disability.[31] As primary headaches are more common in FM, colleagues in primary care and rheumatology need to be further educated about the risk of medication overuse in FM patients from frequent use of analgesics.

Many questions about FM pathophysiology remain unresolved and help to explain the difficulty of a successful therapeutic approach. As in our clinical case, there is growing evidence of cognitive disturbance in FM patients[32] as supported by the voxel basis morphometry results reporting a decrease in gray matter volume in the prefrontal cortex, the amygdala, and the anterior cingulate cortex[33] and the hippocampus dysfunction supported by single-voxel magnetic resonance spectroscopy.[34] While migraine is not a risk factor for cognitive dysfunction or cognitive deterioration over time,[35] neuropsychological investigations highlight frontal lobe-related cognitive impairments in migraineurs including working memory and executive function deficits.[36]

The pattern of generalized cortical hypervigilance and nociceptive cortex hyperactivation and reduced habituation may cause a dissipation of cognitive resources, with high sensitivity to stressful events and focused attention on self-suffering. The pharmacological and nonpharmacological approaches to these aspects are a real challenge for different specialists including headache specialists,

neurologists, psychiatrists, psychologists, and physiatrists to try to lessen the suffering of patients with these disabling disorders.

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