WOMEN AND CHRONIC PAIN

Insights into the physiologic adaptations that predispose women to more frequent, sustained pain events and increased likelihood of chronic pain.

by Keith A. Yount, DDS, FAGD

Neuromuscular problems (neck, back, and head pain) are the second most common pain next to viral- and bacterial-induced pain. Pain in the cervical masticatory muscles (head pain) is one of the most common problems for females.[1] In double-blind, randomized studies, the female-to-male ratio is 3-to-1 for chronic pain in most of the major head and neck pathologies. However, the actual number of women seeking care is closer to 10-to-1, or even as high as 15-to-1 for some chronic pain clinics. In 2001, the ratio of females-to-males requesting examination at Raleigh Facial Pain Services was 84% and in 2002 it was 80%. The exact reasons for this predisposition are difficult to research due to its multiple causes—hormonal influences, central sensitization (rewiring), and sympathetic system changes.

Increasingly, research is linking chronic pain to gender. The study of chronic muscle syndromes, such as myofascial pain, jaw joint pathologies,[2] dysfunction,[3] atypical odontalgia,[4] Meniere's disease,[5] Lupus,[6] burning mouth,[7] and cervical dysfunction,[8] all reveal a strong female predisposition. Some 86% of female chronic pain sufferers in a Swedish study were found to clench or grind their teeth.[9] Tension headache also has a female predominance with 46% of females having frequent tension headache compare to males at 38%.[10] Nearly all the chronic pain syndromes, such as chronic fatigue syndrome, fibromyalgia,[11] and certain malignancies, have a female predominance.[12] Migraines affect 18% of females while only 6% of males.[13] Menstrual migraine is reportedly associated with estrogen fluxes with many of these migraines but typically resolves at menopause.[14]

There are currently three theories for women's predisposition to pain:

1) hormonal differences,
2) rewiring of the nervous system,
3) sympathetic issues.

Hormonal Reasons for Pain

For many years, it has been found that hormone replacement therapy exacerbates migraines.[15] Oral contraceptives change the character and frequency of migraines.[14] In the presence of estrogen, there is a heightened response to neural injury.[16] Mechanical sensitivity of masticatory muscles increases with ovarian hormone fluctuations.[2] In 60% of migraine sufferers, the headache worsens around the premenstrual phase of the menstrual cycle.[18] Fourteen percent of women with migraine experience headache only with the menses.[18] Most women see changes in their headache frequency at puberty and menopause.[19] These numbers provide an obvious relationship between estrogen and chronic pain. Only recently have these pieces of the puzzle about the pathophysiology of women's hormones and headache relationship begun to make sense.

One of the most fascinating research findings in recent years is the estrogen receptor on the female's mast cell. This receptor — genetically coded to provide the female with an inflammation enhancement — is absent in men. The mast cell is a storage tanker for many neurogenic chemicals and is the predominant cell in the inflammation process. When the estrogen levels flux and blood levels of estrogen increase, estrogen couples with the mast cell receptor making it more sensitive to an inflammation stimulus and the dumping of its load of neurogenic chemicals.[20] As it does so, neurogenic chemicals are released more quickly, and with greater numbers of mast cells responding. One of the substances released by the

mast cell is NGF (nerve growth factor)[21] which stimulates production of substance P and VIP (vasoactive intestinal polypeptide)[3] — the main messenger molecules (neurotransmitters) of the pain system. As a result, a female will get more chemicals, more inflammation, more pain, and more swelling from the same stimulus than will a male. This monthly bombardment of neurogenic chemicals takes its toll on the female body. The estrogen-enhanced mast cell inflammation chemical release explains some of the female predominance in the migraine population.

The migraine headache is now thought to be a neurogenic chemical overload that reaches toxic levels in the blood stream going to the brain. The neurogenic chemicals come from a variety of head and neck structures such as muscle and joint over use, sinus infections, ear infections, eye contact with environment, mouth bacterial invasion, and allergies. The main source of this inflammation stimulus is the use of jaw and neck muscles for bad posture, clenching, chewing gum, damaged joints, bad bite, or tension in the muscles. When blood levels of neurogenic inflammation chemicals reach a level that the brain perceives as toxic and threatening to brain safety, the migraine receptor is stimulated to cause vasodilation of blood vessels. This serves to flush toxins away from the brain. The pain from a migraine is mostly from the receptors in the blood vessels that are aggravated due to the stretching caused by this sudden enlargement of the blood vessel. Each person's migraine generator threshold is set at different levels by genetics. It is believed that certain females have a lower setting than others. The neurotransmitter, serotonin, which has long been associated with the migraine headache, varies with the plasma levels of estrogen.[22] The number of serotonin receptors available, it's binding capacities, and its functional status are all associated with estrogen levels.[23] Imitrex is a serotonin mimicking drug used to abort (stop) migraines once they are in full swing.

Further complicating the migraine experience of women is that females exhibit greater sensitivity to laboratory pain as compared to males. Gender differences in pain sensitivity are not site specific, and they seem more noticeable in deep sustained pain sensations similar to the pain of back, neck, and head.[24] Not only are migraines more prevalent in this population but the ensuing pain is felt more intensely.

Estrogen and progesterone also induce increased secretions of prostaglandin, which inhibits central norepinephrine release (a nerve messenger in the pain inhibitory system), antagonizes morphine analgesia (rendering pain pills not as effective), sensitizes pain receptors (more pain receptors react to same stimulus), and increases neurogenic inflammation.[25] This increase in inflammation and pain in the female sets the stage for central nervous system involvement in chronic pain. An increase in stimulus causes an increase in reactivity of the pain system occurring each month. PMS is thought to be nothing more than the side effects of neurogenic chemicals in blood stream.

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Rewiring the Nervous System

Chronic pain has lasting effects on the pain sensing systems. Constant or recurrent pain induces a lowering of the threshold for pain by the pain receptors.[26] The pain system also activates the so-called 'silent nociceptor' in the dorsal horn. One of the mechanisms of wind up is by A-beta fiber glutamate, binding to the AMPA receptor, activating protein kinase, removing Magesium plug, allowing C-fiber glumate to bind to NMDA receptors, allowing inflow Calcium, and thereby turning on these dorsal horn cells for activity.[27] These receptors do not normally react to the environment but, when activated by pain, are brought into action. The pain system then reacts to increasingly smaller and less intense stimuli.

It has been known for years that any increase in stress has no effect on acute pain, but does increase levels of discomfort for those with chronic pain. One may stress a patient that has a toothache or a broken leg and there is no increase in perceived pain levels. If one stresses a patient that has a chronic head or neck pain then there is a sharp increase in perceived pain levels. Normal pain fibers (C-fibers) do not react to stress molecules (adrenalin). Pain causes alpha-1 receptors to be produced and transported to C-fiber terminals.[28] These receptors are sensitive to adrenalin produced by the sympathetic system when the body is under stress and the pain fibers (that usually respond only to pain stimulus) will now respond to stress stimulus. This is thought to be a protective mechanism to help the body avoid more painful stimulus in order to heal. Yet the typical sufferer does not heed the message but keeps on with problematic life styles, behaviors, and habits. Unfortunately, chronic pain also makes the muscle pain receptors more sensitive to stress, anxiety, and depression.[29]

Painful stimulus such as a damaged joint, overused muscle, or any bacterial invasion induces mast cells to release their load of chemicals. Included in this inflammation soup is Nerve Growth Factor (NGF).[21] NGF stimulates new growth of nerve fibers which is necessary for healing, but it also stimulates nerve growth that is part of enhanced pain reporting. One enhancement is the sprouting of sympathetic fibers in the dorsal horn to connect to pain system nerves (C-fibers).[30] The stress system thus gets a direct wiring to the pain system. This is another reason why stress has a relationship to chronic pain but not to acute pain and why touch and pressure can create pain in chronic pain patients.

The purpose of the adaptive response to pain is to limit activity to allow healing, but when it is over-stimulated; this pain adaptation becomes part of the pain syn-

drome. It is also hard to limit activity in the head region due to its importance to life. The central pain system is affected by the peripheral adaptive system of the nervous system. The longer pain is present, the more sensitive the pain reporting system.

Sympathetic (Stress) Reasons for Pain

Muscle pathologies such as neck aches, backaches, and headaches are definitely more predominant in females. Each of these muscle-based pathologies shows a relationship between pain and an increase in stress. The stress (perceived danger) activates the sympathetic system which causes a nerve impulse to travel down the sympathetic pathway (called the gamma efferent nerve fiber) to muscle.[29,31] These nerve fibers activate muscle spindles to prepare the muscle to move in response to perceived danger. Unfortunately, most stress situations — such as a reckless driver pulling out in front of you and causing a near collision — do not resolve in a "fight or flight" muscle movement. Over prolonged and frequent stimulation, the muscle spindle becomes damaged and enlarged and subsequently causes a sustained contraction of the smooth muscle of the muscle spindle. The over-stimulation of the sympathetic system (protection system) creates the onus for these damaged smooth muscle fibers and is referred to as a trigger point. Recent research reveals evidence that damaged muscle tissues (trigger points) are muscle spindles under the control of the sympathetic system.[32] In one study, sympathetic blocking agents (phentolyamine) injected into the trigger point blocked the pain, but the skeletal blocking agents (curare or botox) did not block the pain.[33]

The amount of neurogenic chemicals in the muscle and the extra workload due to painful muscle splinting creates the environment for damaged muscle fibers. Muscle pathology is set off by increased inflammation in muscles during estrogen fluxes. The pain from increased swelling and muscle pain causes more muscle contraction and an increase in muscle tone. Trigger points develop which become the sources of neurogenic stimulation of the pain system. The inflammation, swelling, and pain gradually induce less exercise, poor sleep, and additional pain.

Chronic muscle pathologies such as fibromyalgia, chronic fatigue syndrome, myofascial pain syndrome, and tension headache all have trigger points associated with them. The muscle-based pathologies are difficult to diagnose because they can refer pain to distant areas. A good example of this is a heart attack that feels like indigestion. These trigger point referral patterns, outlined by Travell & Simon,[34] are now used in chronic pain diagnosis as a way to identify the correct site of the pain source. Travell & Simon also make the critical observation that deep muscle pain is not location-specific in the brain. In other words, the perceived site of pain may be different from the actual source of pain. Travell and Simon's book outlines trigger points' distinct patterns of referral. For example, the atypical earache may have referred pain from other locations and the atypical toothache may be referred pain from muscles. This is important in diagnosing women since muscle-based pathologies are more prominent and prevalent in this group.

During over-stimulation of the muscles in females, it is observed that the sympathetic system is enhanced, more reactive, and more sustained. The female sympa-

thetic system is enlarged (amygdyla) and more responsive to stimuli. The "lower highway" — the primitive protective system — is enhanced in females that have been subjected to verbal, physical, or sexual abuse. This phenomena is summed up in the term "emotional hijacking" used by Daniel Goleman in his book *Emotional Intelligence*.[35] The female species seems more prone to taking on the cares of the world, family, society, church, community, and world — especially after they become mothers.

The over-stimulation of the sympathetic system begins to set the stage for autonomic system imbalance. When one side of the system is dominant, the other is recessive. The parasympathetic system is in charge of life support systems and the sympathetic is in charge of protection. Conservation of resources allows for use of one system more than another. When we over stimulate the sympathetic system, the parasympathetic system is suppressed. The longer the perceived danger or stress, the less the life support systems work correctly and eventually sleep and digestive systems begin to malfunction. Slowly, progressively, and insidiously, sleep quality goes down with increase awakening, slower sleep onset, and awakening unrefreshed. A key goal must be to improve the balance of the autonomic system.

Summary

The longer a pain continues, the greater the increase in maladaptation of the nervous system, including sympathetic sprouting, a-Beta fibers connecting to C-fibers, activation of silent pain receptors, Apha-1 receptor production, trigger point development, increased inflammatory chemicals, emotional hijacking, and autonomic system imbalance. The resulting pain precipitates a cascade of less exercise, poor sleep, malabsorption of nutrients, stress, depression, and pain. In this vicious cycle, pain becomes even more stubborn, refractory, and multifaceted — especially given the physiologic predisposition of women. Pain must be treated early and aggressively — especially in women — to avoid devolution into a chronic pain state. ■

Keith A. Yount, DDS, FAGD, is in practice at Raleigh Facial Pain Services in Raleigh, North Carolina. A diplomate of the American Board of Orofacial Pain, Dr. Yount received his DDS from the University of North Carolina, Chapel Hill. In addition to lecturing on chronic pain, he also has written articles on this subject for several publications. Dr. Yount can be reached at 4505 Fairmeadow Lane, Ste 207, Raleigh, NC 27607.

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