

## Glial Cell Activation and Neuroinflammation: How They Cause Centralized Pain

Glial cell activation and neuroinflammation are the underlying causes of centralized pain and its associated comorbidities, including depression, fatigue, and insomnia.

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Glial cell activation and neuroinflammation are known to be one of the underlying causes of centralized pain (CP) and many of its comorbidities, including depression, fatigue, and insomnia.<sup>1-4</sup> Activation of glial cells leads to an ongoing pathologic process in the central nervous system (CNS) that includes neuroinflammation, glial cell dysfunction (GCD), cellular destruction, hyperarousal of the sympathetic nervous system, and stimulation of the hypothalamic-pituitary complex.<sup>5-15</sup>

Pain that initially arises from a peripheral nervous system injury may become imprinted or “embedded” in the CNS. This phenomenon is called “central sensitization,” and the resulting state is CP.<sup>13-16</sup> Phantom limb pain is the classic example. Other examples include neuropathies, including complex regional pain syndrome and diabetic neuropathies.

In this review, I will explain how glial cell activation and neuroinflammation occur and review their clinical ramifications to provide the pain practitioner with a status report on what is known about this pathologic process.

### How Glial Cells Malfunction

The CNS is comprised of neurons that transmit pain signals as well as 3 basic types of glia cells: microglia, astrocytes, and oligodendrocytes (Table 1). Neurons in the CNS are surrounded by glial cells whose primary function is to support, protect, and nurture the neurons through mediators involved in energy transfer and processes essential to neural plasticity and stability.<sup>7,17,18</sup> Microglia cells migrate to the CNS during prenatal development. They are the resident immune cells in both the brain and spinal cord and are vigilant for any type of toxic challenge, including injury, infection, and ischemia (Table 2).<sup>7-10,17,18</sup> Once activated, they take on a role similar to that of a peripheral macrophage, in that, they enlarge, migrate, and can become phagocytic and remove toxic matter.<sup>9,10,17</sup> If the microglia cells cannot resolve or eliminate a toxic insult in the CNS, they remain reactive and recruit astrocytes and oligodendrocytes into an ongoing inflammatory process (Table 3).<sup>4,8,19,20</sup> Glutamate, an important neurotransmitter, and neurotoxins are released during neural injury. Even neurons may be recruited and trapped in the neuroinflammatory process. The anatomic size and site of inflammation and dysfunction that results from glial cell activation may vary in the brain; multiple anatomic areas have been implicated.<sup>14,15</sup> Magnetic resonance imaging (MRI) scans of the brain of patients with CP show areas of varying cellular dysfunction and/or destruction.<sup>21-27</sup> Symptoms and comorbidities may vary depending on the CNS location and severity of the inflamed site.<sup>3,28,29</sup>

After microglia activate and neuroinflammation begins, the autonomic, sympathetic nervous system is stimulated and the hypothalamic-pituitary complex is aroused<sup>5,14-16</sup> and the CNS may become overly sensitive to pain (central sensitization).<sup>30</sup> The CNS attempts to heal or reform itself and eliminate the pathologic process.<sup>5,6</sup> This reformation or reshaping of CNS tissue is referred to as neuroplasticity.<sup>30</sup> The neuroplastic response is believed by some observers to be the mechanism that captures or traps the memory of pain. Activated microglial cells and neuroinflammation can release at least 30 different molecular mediators, some pro-inflammatory and others anti-inflammatory.<sup>17,31-34</sup> Some of these mediators enter the blood circulation and can be measured.<sup>35,36</sup>

Schwann cells are a fourth type of glial cell located in the peripheral nervous system, whose primary function is supply the myelin to surround and insulate the axons of the peripheral neurons.<sup>37</sup> When a peripheral injury occurs, Schwann cells proliferate, migrate, and secrete numerous factors including pro-inflammatory cytokines.<sup>37</sup> It is generally thought that various mediators and/or electrical signals from an injury site travel retrograde up neurons to activate microglia in the CNS and initiate the neuroinflammatory process. Schwann cells undoubtedly participate in signaling microglia, but the mechanism is unclear.<sup>19,37</sup>

#### Which Pain States are Involved?

Any pain state that becomes centralized in the CNS apparently is the product of and/or is associated with microglial activation, neuroinflammation, and GCD.<sup>11-14</sup> Patients who have been labeled as having central pain syndrome have been victims of a lesion or injury in the spinal cord, brainstem, or cerebral hemisphere(s).<sup>15</sup> These lesions or injuries can be caused by stroke, multiple sclerosis, Parkinson's disease, encephalitis, and traumatic brain injury, among other neurologic diseases. Nerve injury in the periphery, such as discogenic spine degeneration, neuropathies, and arthropathies, also may activate microglial cells in the CNS to induce neuroinflammation.<sup>14,15</sup> Even after the peripheral nerve injury is healed, CP may endure and become permanent (Figure 1). A third group of pain patients who may have neuroinflammation and GCD are those who have fibromyalgia, interstitial cystitis, and vulvodynia.<sup>25</sup> These conditions are believed by many observers to arise, de novo, in the CNS.

## Clinical Profile of CP

Regardless of the initial cause of pain, CP produces a rather typical clinical profile.<sup>16</sup> The terms central pain, central pain syndrome, centralized pain, central sensitization, and central neuropathic pain all have been used to describe the profile.<sup>15</sup> The cardinal complaint of CP patients is that their pain is constant (“never leaves”). The hypersensitivity, or sensitization, of CP causes the patient to over-perceive pain from peripheral stimuli.<sup>30,38-40</sup> Patients often will report typical symptoms of allodynia, hyperthermia, hyperhidrosis, anxiety, fatigue, insomnia, anorexia, and depression. Physical signs are those of sympathetic over-stimulation and include mydriasis, tachycardia, hypertension, hyperreflexia, hyperhidrosis, and vasoconstriction (eg, cold extremities). Table 4 summarizes many of the clinical manifestations of CP. When a patient has a preponderance of these manifestations, they should be given the clinical diagnosis of CP.

## Depression and CP

Depression and pain long have been known to be inextricably intertwined.<sup>41-52</sup> Severe chronic pain patients are almost universally depressed, and some depressed patients develop pain after the onset of depression.<sup>43,48</sup> People with chronic pain are reported to have 3 times the average risk for developing psychiatric symptoms—usually mood or anxiety disorders—and depressed patients have 3 times the average risk for developing chronic pain.<sup>5,48</sup> Symptom profiles and comorbidity of CP and depression are extremely similar, in that many CP and depressed patients report insomnia, fatigue, intellectual impairment, anxiety, eating disorders (eg, anorexia or obesity), and reclusivity.<sup>43,45,51</sup> So similar and over-lapping are these conditions that antidepressants have become a first-line treatment for both.

Comorbid depression and pain are prevalent with diseases that have elevated levels of inflammation, such as rheumatoid arthritis, cancer, and Alzheimer’s disease.<sup>51-54</sup> This finding helped lead to investigations into how immune cells and glial cells interact with neurons to alter pain sensitivity and to mediate the transition from acute to chronic pain. Just as glial cells become activated after a peripheral nerve injury, multiple studies also suggest that glial cell activation, glutamate release, inflammation, and GCD contribute to the pathophysiology of depression.<sup>29</sup> Both CP and depression are conditions that are known to be associated with underlying neuroinflammation and GCD.<sup>3,29,31,37,38,55</sup>

## Other Comorbidities

The realization that CP is based on neuroinflammation and GCD provides a better understanding of the close relationship of CP and depression, as well as symptoms of insomnia, fatigue, anxiety, and mental impairments. Other mood disorders, including post-traumatic stress disorder, anxiety, and manic depressive disorder, that commonly occur with chronic pain states also may be related to neuroinflammation.<sup>28,29,40,42</sup> Although not completely clear, the close association and temporal relationship between CP and mood disorders strongly suggests that neuroinflammation and GCD are the major underlying factors in such conditions as post-traumatic stress disorder. It may well be that childhood abuse, sexual or otherwise, and other CNS insults that occur long before clinical symptoms of depression or CP may set up an inflammatory focus or propensity that contributes to these conditions in later life. This is easy to comprehend, considering that neuroinflammation is a focus of cellular dysfunction and destruction that may affect various parts of the CNS, may spread in a random, uncontrolled fashion, and may produce a variety of clinical manifestations.

## Search for Serum Biomarkers

The author has attempted to identify serum biomarkers that may corroborate the clinical diagnosis of CP. A number of biomarkers are available for major depressive disorder (MDD) that, in effect, are measuring the presence of glial cell activation and neuroinflammation.<sup>35,36</sup> Objective biomarkers that help document the presence of CP are most welcome, because CP requires a different treatment approach than simple, peripheral pain.

In one investigation, I studied 39 CP patients who were receiving ongoing medical management with opioids and a variety of ancillary agents and who exhibited the clinical profile of CP.<sup>55</sup> Serum samples were simultaneously measured for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP),  $\alpha$ -1-antitrypsin, myeloperoxidase, and soluble tumor necrosis factor- $\alpha$  receptor Type II. All 5 of these serum markers are known to reflect the presence of inflammation, although the site of the inflammation cannot be determined precisely from a serum sample.<sup>36,56</sup> Over half of the patients (22; 56.4%) demonstrated at least 1 elevated biomarker. No specific biomarker was particularly dominant; each was elevated in at least 5 patients (12.8%) in treatment.

In another group of patients, I studied serum elevations of some pituitary hormones that are known to elevate in pain or depression states.<sup>35,36</sup> These included adrenocorticotrophic hormone (ACTH), prolactin, and epidermal growth factor (EGF). Elevations of ACTH were found in 4 of 47 patients (8.5%), elevations of prolactin in 11 of 80 patients (13.8%), and elevations of EGF in 5 of 80 patients (6.3%).

Based on my early observations, I postulate that neuroinflammation likely is the same basic process as peripheral inflammation that occurs in muscle or joints. This belief possibly is supported by the fact that microglia actually are macrophages that enter the CNS from the peripheral circulation during

embryogenesis and are not innate cells of the CNS. Also, the ESR and CRP appear to elevate from both peripheral and central sources.<sup>56</sup>

Many mediators are involved in all inflammatory reactions including neuroinflammation.<sup>31-34</sup> Consequently, at this time, no one mediator that is specifically diagnostic of CP can be selected. Because CP causes stimulation of the hypothalamic-pituitary complex, elevation of some pituitary hormones is to be expected and serves as a biomarker of CP. There has not, however, been consistency as to which inflammatory biomarkers or pituitary hormones will be elevated in CP patients. At this time, therefore, no single biomarker is recommended to help make the diagnosis of CP. The best that can be said is that elevations of some inflammatory mediators and pituitary hormones support the presence of CP but are not diagnostic of it. For adventuresome practitioners, a reasonable approach is to test CP patients for elevations of ESR, CRP, prolactin, and ACTH. These laboratory tests are easily accessible today through any commercial laboratory.

## Summary

Glial cell activation may produce a number of pathologic sequelae in the CNS, including neuroinflammation, cellular destruction, GCD, stimulation of the sympathetic nervous system, and hyperarousal of the hypothalamic-pituitary complex. The memory of pain may be trapped, or centralized, in this pathologic process, and several comorbidities, including depression, fatigue, anxiety, and insomnia, may result. The diagnosis of CP is a clinical one, based on history and physical findings that result from glial cell activation and neuroinflammation. There is no single biomarker that is diagnostic of CP, but some inflammatory mediators and pituitary hormones may be elevated in the serum of patients with glial cell activation and neuroinflammation. When these inflammatory mediators and hormones are found, they help support a clinical diagnosis of CP.

## References

Watkins LR, Maier SF. When good pain turns bad. *Curr Dir Psychol Sci.* 2003;12(6):232-236.

Tracey I, Bushnell CM. How neuroimaging studies have challenged us to rethink is chronic pain a disease? *J Pain.* 2009;10(11):1113-1120.

Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. Neuroinflammation and comorbidity of pain and depression. *Pharmacol Rev.* 2014;66(1):80-101.

Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? *Pain.* 2013;154(suppl 1):s10-s28.

Henry DE, Chiodo AE, Yan W. Central nervous system reorganization in a variety of chronic pain states: a review. *PM R*. 2011;3(12):1116-1125.

May A. Chronic pain may change the structure of the brain. *Pain*. 2008;137(1):7-15.

Graeber MB, Streit WJ. Microglia: biology and pathology. *Acta Neuropathol*. 2010;119(1):89-105.

Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. *Nat Rev Neurosci*. 2009;10(1):23-36.

Kraft AD, Harry GJ. Feature of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. *Int J Environ Res Public Health*. 2011;8(7):2980-3018.

Rock RB, Gekker G, Hu S. et al. Role of microglia in central nervous system infections. *Clin Microbiol Rev*. 2004;17(4):942-964.

Vera-Portocarrero LP, Zhang ET, Ossipov MG, et al. Descending facilitation from the rostral ventromedial medulla maintains nerve injury-induced central sensitization. *Neuroscience*. 2006;140(4):1311-1320.

Wang R, King T, DeFelcie M, Guo W, Ossipov MH, Porreca F. Descending facilitation maintains long-term spontaneous neuropathic pain. *J Pain*. 2013;14(8):845-853.

Graeber MB, Christei MJ. Multiple mechanisms of microglia: a gatekeeper's contribution to pain states. *Exp Neurol*. 2012;234(2):255-261.

Calvo M, Bennett DL. The mechanism of microgliosis and pain following peripheral nerve injury. *Exp Neurol*. 2012;234(2):271-282.

Finnerup NB. A review of central neuropathic pain states. *Curr Opin Anaesthesiol*. 2008;21(5):586-589.

Tennant F. Centralized pain: our new clinical challenge. *Pain Week*. 2013;1:11-14.

Graeber MB. Changing face of microglia. *Science*. 2010;330(6005):783-788.

Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *J Neurosci*. 2009;29(13):3974-3980.

Gwak YS, Hulsebosch CE. Remote astrocytic and microglial activation modulates neuronal hyperexcitability and below-level neuropathic pain after spinal injury in rat. *Neuroscience*. 2009;161(3):895-903.

Obata H, Sakurazawa S, Kimura M, Saito S. Activation of astrocytes in the spinal cord contributes to the development of bilateral allodynia after peripheral nerve injury in rats. *Brain Res*. 2010;1363:72-80.

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiol Clin*. 2000;30(5):263-288.

Rodriguez-Raecke R, Niemieier A, Ihle K, Ruether W, May A. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *J Neurosci*. 2009;29(44):13746-13750.

Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci*. 2004;24(46):10410-10415.

Teutsch S, Herken W, Bingel U, Schoell E, May A. Changes in brain gray matter due to repetitive painful stimulation. *Neuroimage*. 2008;42(2):845-849.

Kuchinad A, Schweinhardt DA, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia. *J Neurosci*. 2007;27(15):4004-4007.

Buckalew N, Haut MW, Morrow L, Weiner D. Chronic pain is associated with brain volume loss in older adults: preliminary evidence. *Pain Med*. 2008;9(2):240-248.

Robinson ME, Craggs JG, Price DD, Perlstein WM, Staud R. Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. *J Pain*. 2011;12(4):436-443.

Asmundson GJ, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depress Anxiety*. 2009;26(10):888-901.

Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflammation*. 2013;10:43.

Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895-926.

Stein A, Panjwani A, Sison C, et al. Pilot study: elevated circulating levels of the pro-inflammatory cytokine macrophage migration inhibitory factor in chronic spinal cord injury patients. *Arch Phys Med Rehabil*. 2013;94(8):1498-1507.

Thompson CD, Zurko JC, Hanna BF, Hellenbrand DJ, Hanna A. The therapeutic role of interleukin-10 after spinal cord injury. *J Neurotrauma*. 2013;30(15):1311-1324.

Whitehead KJ, Smith CB, Delaney SA, et al. Dynamic regulation of spinal pro-inflammatory cytokine release in the rat in vivo following peripheral nerve injury. *Brain Behav Immun*. 2010;24(4):569-576.

Zhou Z, Peng X, Insolera R, Fink DJ, Mata M. IL-10 promotes neuronal survival following spinal cord injury. *Exp Neurol*. 2009;220(1):183-190.

Smith, KM, Renshaw, PF, Bilello, J. The diagnosis of depression: current and emerging methods. *Compr Psychiatry*. 2013;54(1):1-6.

Papakostos G, Shelton RS, Kinrys G, et al. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. *Mol Psychiatry*. 2013;18(3):332-339.

Campara WM. Schwann cells: activated peripheral glia and their role in neuropathic pain. *Brain Behav Immun*. 2007;21(5):522-527.

Mika J. Modulation of microglia can alternate neuropathic pain symptoms and enhance morphine effectiveness. *Pharmacol Rep*. 2008;60(3):297-307.

Hains LE, Loram LC, Weiseler JL, et al. Pain intensity and duration can be enhanced by prior challenge: initial evidence suggestive of a role of microglial priming. *J Pain*. 2010;11(10):1004-1014.

Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systemic review. *JAMA*. 2008;300(6):711-719.

Arnou BA, Blasey CM, Lee J, et al. Relationships among depression, chronic pain, chronic disabling pain, and medical costs. *Psychiatr Serv*. 2009;60(3):344-350.

McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain*. 2004;111(1-2):77-83.

Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163(20):2433-2445.

Bair MJ, Robinson RL, Eckert GJ, Stabg OE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. *Psychosom Med*. 2004;66(1):17-22.

Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003;60(1):39-47.

Ericsson M, Poston WS, Linder J, Taylor JE, Haddock CK, Foreyt JP. Depression predicts disability in long-term chronic pain patients. *Disabil Rehabil*. 2002;24(6):334-340.

Robinson MJ, Edwards SE, Iyengar S, Bymaster F, Clark M, Katon W. Depression and pain. *Front Biosci*. 2009;14:5031-5051.

Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain*. 1997;13(2):116-137.

Rudy TE, Kerns RD, Turk DC. Chronic pain and depression: toward a cognitive-behavioral mediation model. *Pain*. 1988;35(2):129-140.

Turk DC, Okifuji A, Scharff L. Chronic pain and depression: role of perceived impact and perceived control in different age cohorts. *Pain*. 1995;61(1):93-101.

McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain*. 2004;111(1-2):77-83.

Kojima M, Kojima T, Suzuki S, et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. *Arthritis Rheum*. 2009;61(8):1018-1024.

Rakoff-Nahoum S. Why cancer and inflammation? *Yale J Biol Med*. 2006;79(3-4):123-130.

Nagele RG, D'Andrea MR, Lee H, Venkataraman V, Wang HY. Astrocytes accumulate A $\beta$  42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. *Brain Res*. 2003;971(2):197-209.

Tennant F. Search for inflammatory markers in centralized, intractable pain. Presented at: American Academy of Pain Management. September 2013;Orlando, Florida.

Tennant F. Erythrocyte sedimentation rate and C-reactive protein: old but useful biomarkers for pain treatment. *Pract Pain Manage*. 2013;13(2):61-65. [View Sources](#)

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