Published in final edited form as:

J Hand Surg Am. 2009 September ; 34(7): 1334–1336. doi:10.1016/j.jhsa.2009.04.003.

Cutaneous Neuroma Physiology and Its Relationship to Chronic Pain

Catherine Curtin, MD and Ian Carroll, MD

Division of Plastic Surgery, Stanford University, Palo Alto, CA; Palo Alto Veteran's Hospital, Palo Alto, CA; Department of Anesthesia, Stanford University, Palo Alto, CA

Unremitting pain after uncomplicated hand surgery can frustrate both surgeon and patient. For example, the incidence of surgical site pain after carpal tunnel release has been estimated to be as high as 59% by some.^{1–3} This pain may be incisional, periincisional (so-called “pillar” pain), or in the distribution of the cutaneous supply of the median nerve.^{4,5} Although the reasons behind postoperative chronic pain are multifactorial, one cause may be entrapment of cutaneous nerve in the surgical scar. As we will describe, cutaneous nerve entrapment can result in deep, diffuse pillar pain.

On presentation, the symptoms of cutaneous nerve injury may be nonfocal and may present a diagnostic dilemma. Some patients present with the classic Tinel sign or scar dysesthesia; however, on occasion the patient complains of vague pain that is not isolated to a single peripheral nerve distribution. These seemingly nonanatomic symptoms are secondary to a host of pathologic changes that occur in response to nerve injury and that are becoming clear with ongoing pain research.

Nociceptors are a special subset of sensory neurons that transduce the sensation of pain. At baseline, these nociceptors only reach action potentials and fire when subjected to high levels of stimuli (usually close to the amount of stimulation associated with tissue injury).⁶ Several authors have demonstrated that trauma to these nerves can alter their phenotype. After injury, these nerves demonstrate up-regulation of sodium channels,^{7,8} adrenergic receptors,^{9–12} and nicotinic cholinergic receptors.¹³ These up-regulated proteins generate depolarizing currents that can confer a pacemaker-like effect to the nociceptors, which will then repetitively depolarize and cause the transmission of an action potential in the absence of external stimuli.

The unrelenting barrage of nerve impulses from injured peripheral nociceptors increases the excitability of adjacent uninjured pain-transmitting neurons in the spinal cord. This is called *central sensitization*.^{6,14} Multiple levels of the spinal cord can be activated in central sensitization because incoming peripheral sensory fibers can cross several spinal segments before finally synapsing with their second-order neurons in the dorsal gray matter of the ipsilateral spinal cord.^{15,16} For example, axonal fibers of the ulnar nerve enter the cord at C8 and T1. Yet, the ulnar nerve has been shown to have synapses with second-order neurons in both higher and lower spinal segments, including C6 and C7—areas that are stimulated by fibers of both the median and radial nerves. An injury to a terminal cutaneous branch of the ulnar nerve can result in central sensitization that spans multiple spinal segments and can therefore cause pain to be perceived in both the median and radial nerve distributions.

The pain pathways are complex, and at each level physiologic changes can occur with chronic pain. The nociceptors primarily synapse in the dorsal horn of the spinal cord, and then the pain signal ascends via the spinothalamic tract diverging at the thalamus. Separate neuroanatomic pathways regulate the sensory–intensity and affective–unpleasantness components of pain. The ventrolateral posterior thalamic nucleus and somatosensory cortex provide information on where the pain is, how much area it covers, and what it feels like. Other areas including the ventromedial posterior thalamic nucleus and its cortical connections create the affective/motivational aspects of pain; for example, the “aversiveness” of the sensation, the drive to escape, and fear of the pain.^{17–19} The anatomy is such that the more intense the pain becomes, the more it will be perceived in a poorly localized way. This is due to the recruitment of second-order neurons that under normal circumstances represent other anatomic areas in neighboring spinal segments. This physiology may explain the “spreading” of pain seen in patients with complex regional pain syndrome in which neuralgic pain crosses boundaries defined by peripheral nerve distributions. These physiologic changes also ensure that many patients with cutaneous nerve injuries and “scar neuromas” complain not of superficial shooting or electrical pain at the scar but rather deep, diffuse, poorly localized, aching or throbbing pain that the patient may only occasionally localize to the scar. Patients therefore attribute their sense of deep, persistent, poorly localized pain to ongoing pathology in the area that was the target of the original surgery; in actuality, their pain is pathologic activation of both peripheral and central pain pathways.

The diagnosis of this problem is made through an appreciation of the functional neuroanatomy and a high level of vigilance. If the surgeon suspects a cutaneous neuroma, intradermal injection of the scar with lidocaine will be diagnostic. After injection, the patient will get instant relief, generally encompassing the whole area of their pain including the areas that seem to be in another nerve’s distribution. Treatment, however, is not as clear, as both surgical and nonsurgical interventions have been described with varying degrees of success.^{20,21}

Most surgical approaches share in common a resection of the cutaneous nerve, suggesting that cutaneous scar may represent a uniquely bad place for an injured nerve.^{22,23} The skin itself is richly innervated with adrenergic and cholinergic efferents from the sympathetic and parasympathetic nervous systems, and in this environment, increased expression of adrenergic receptors and nicotinic cholinergic receptors on injured peripheral nerve endings results in increased pain and firing rates of the nociceptive neurons.^{12,13,24,25} As yet, no surgical standard has emerged.

Nonsurgical approaches to the cutaneous neuroma have included injection of neurolytic solutions in various formulations,^{26,27} spinal cord stimulation,^{28,29} peripheral nerve stimulation,^{30,31} local anesthetics, and botulinum toxin.³² Botulinum toxin inhibits acetylcholine release from cholinergic nerves in the skin in a long-standing, but ultimately fully reversible, manner.³³ It may work by decreasing stimulation of nicotinic cholinergic receptors on injured nociceptors or through other mechanisms such as inhibition of calcitonin gene-related peptide release from nociceptors.^{34,35} If proven effective, botulinum toxin may have advantages over previous neurolytic techniques because of an improved safety profile. Botulinum toxin has less risk of worsening symptoms in a permanent way and there is a decreased incidence of skin breakdown when compared to the injection of more caustic substances such as alcohol.

Future research will continue to focus on understanding the transformation of some cutaneous nerves into sources of chronic pain. The fact that most traumas including surgery do not result in chronic pain indicates that the majority of cutaneous nerve injuries do not transform into chronic pain centers. Some evidence indicates that the central nervous system’s responses to injury may be as critical as the mode of injury in ultimately determining clinical outcome with

respect to pain.^{36–38} Within this context, the next horizon is to assess if we can therapeutically target the central nervous system response to injury to reduce the incidence of posttraumatic chronic pain. Pilot studies in humans indicate that ketamine,³⁹ intrathecal clonidine,⁴⁰ and epidural local anesthetic⁴¹ each when given at the time of injury may reduce the proportion of patients who go on to have chronic postsurgical pain. Animal studies further suggest that medications such as the antibiotic minocycline, which also has glial cell inhibitory properties, may prevent the development of chronic nerve pain when given at the time of, but not after, injury.³⁸ Further understanding of the perioperative central nervous system response to nerve trauma and head-to-head studies comparing techniques to prevent and treat scar neuromas hold promise to improve surgical outcomes and reduce postoperative morbidity.

Acknowledgments

Supported by a VA Career Development Award (C.C.).

References

1. Boya H, Ozcan O, Oztekin HH. Long term complications of open carpal tunnel release. *Muscle Nerve* 2008;38:1443–1446. [PubMed: 18949783]
2. Brown RA, Gelberman RH, Seiler JG III, Abrahamsson SO, Weiland AJ, Urbaniak JR, et al. Carpal tunnel release: a prospective randomized assessment of open and endoscopic methods. *J Bone Joint Surg* 1993;75A:1265–1275. [PubMed: 8408148]
3. Kluge W, Simpson RG, Nicol AC. Late complications after open carpal tunnel decompression. *J Hand Surg* 1996;21B:205–207.
4. Yung PS, Hung LK, Tong CW, Ho PC. Carpal tunnel release with a limited palmar incision: clinical results and pillar pain at 18 months follow-up. *Hand Surg* 2005;10:29–35. [PubMed: 16106498]
5. Thoma A, Veltri K, Haines T, Duku E. A systematic review of reviews comparing the effectiveness of endoscopic and open carpal tunnel decompression. *Plast Reconstr Surg* 2004;113:1184–1191. [PubMed: 15083019]
6. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000;288:1765–1769. [PubMed: 10846153]
7. Hains BC, Klein JP, Saab CY, Craner MJ, Black JA, Waxman SG. Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. *J Neurosci* 2003;23:8881–8892. [PubMed: 14523090]
8. Pertin M, Ji RR, Berta T, Powell AJ, Karchewski L, Tate SN, et al. Upregulation of the voltage-gated sodium channel beta2 subunit in neuropathic pain models: characterization of expression in injured and non-injured primary sensory neurons. *J Neurosci* 2005;25:10970–10980. [PubMed: 16306410]
9. Perl ER. Causalgia, pathological pain, and adrenergic receptors. *Proc Natl Acad Sci U S A* 1999;96:7664–7667. [PubMed: 10393877]
10. Xie J, Ho Lee Y, Wang C, Mo Chung J, Chung K. Differential expression of alpha1-adrenoceptor subtype mRNAs in the dorsal root ganglion after spinal nerve ligation. *Brain Res Mol Brain Res* 2001;93:164–172. [PubMed: 11589993]
11. Drummond PD, Finch PM, Skipworth S, Blockey P. Pain increases during sympathetic arousal in patients with complex regional pain syndrome. *Neurology* 2001;57:1296–1303. [PubMed: 11591852]
12. Ali Z, Raja SN, Wesselmann U, Fuchs PN, Meyer RA, Campbell JN. Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. *Pain* 2000;88:161–168. [PubMed: 11050371]
13. Vincler M, Wittenauer S, Parker R, Ellison M, Olivera BM, McIntosh JM. Molecular mechanism for analgesia involving specific antagonism of alpha9alpha10 nicotinic acetylcholine receptors. *Proc Natl Acad Sci U S A* 2006;103:17880–17884. [PubMed: 17101979]
14. Ikeda H, Stark J, Fischer H, Wagner M, Drdla R, Jager T, et al. Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science* 2006;312:1659–1662. [PubMed: 16778058]

15. Traub RJ, Allen B, Humphrey E, Ruda MA. Analysis of calcitonin gene-related peptide-like immunoreactivity in the cat dorsal spinal cord and dorsal root ganglia provide evidence for a multisegmental projection of nociceptive C-fiber primary afferents. *J Comp Neurol* 1990;302:562–574. [PubMed: 1702117]
16. Ling LJ, Honda T, Shimada Y, Ozaki N, Shiraishi Y, Sugiura Y. Central projection of unmyelinated (C) primary afferent fibers from gastrocnemius muscle in the guinea pig. *J Comp Neurol* 2003;461:140–150. [PubMed: 12724833]
17. Mackey SC, Maeda F. Functional imaging and the neural systems of chronic pain. *Neurosurg Clin N Am* 2004;15:269–288. [PubMed: 15246336]
18. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769–1772. [PubMed: 10846154]
19. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277:968–971. [PubMed: 9252330]
20. Wu J, Chiu DT. Painful neuromas: a review of treatment modalities. *Ann Plast Surg* 1999;43:661–667. [PubMed: 10597831]
21. Lewin-Kowalik J, Marcol W, Kotulska K, Mander M, Klimczak A. Prevention and management of painful neuroma. *Neurol Med Chir (Tokyo)* 2006;46:62–67. [PubMed: 16498214]
22. Vernadakis AJ, Koch H, Mackinnon SE. Management of neuromas. *Clin Plastic Surg* 2003;30:247–268.
23. Hazari A, Elliot D. Treatment if end neuromas, neuromas in continuity and scarred digits by proximal relocation. *J Hand Surg* 2004;29B:338–350.
24. Chabal C, Jacobson L, Russell LC, Burchiel KJ. Pain response to perineuromal injection of normal saline, epinephrine, and lidocaine in humans. *Pain* 1992;49:9–12. [PubMed: 1594285]
25. Choi B, Rowbotham MC. Effect of adrenergic receptor activation on post-herpetic neuralgia pain and sensory disturbances. *Pain* 1997;69:55–63. [PubMed: 9060013]
26. Defalque RJ. Painful trigger points in surgical scars. *Anesth Analg* 1982;61:518–520. [PubMed: 7200742]
27. Kirvela O, Nieminen S. Treatment of painful neuromas with neurolytic blockade. *Pain* 1990;41:161–165. [PubMed: 2367142]
28. Maeda Y, Wacnik PW, Sluka KA. Low frequencies, but not high frequencies of bi-polar spinal cord stimulation reduce cutaneous and muscle hyperalgesia induced by nerve injury. *Pain* 2008;138:143–152. [PubMed: 18207326]
29. Sindou MP, Mertens P, Bendavid U, Garcia-Larrea L, Mauguire F. Predictive value of somatosensory evoked potentials for long-lasting pain relief after spinal cord stimulation: practical use for patient selection. *Neurosurgery* 2003;52:1374–1383. [PubMed: 12762882]
30. Stregde DW, Cooney WP, Wood MB, Johnson SJ, Metcalf BJ. Chronic peripheral nerve pain treated with direct electrical nerve stimulation. *J Hand Surg* 1994;19A:931–939.
31. Mobbs RJ, Nair S, Blum P. Peripheral nerve stimulation for the treatment of chronic pain. *J Clin Neurosci* 2007;14:216–221. [PubMed: 17258129]
32. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type a induces direct analgesic effects in chronic neuropathic pain. *Ann Neurol* 2008;64:274–283. [PubMed: 18546285]
33. Schiavo G, Matteoli M, Montecucco C. Neurotoxins affecting neuroexocytosis. *Physiol Rev* 2000;80:717–766. [PubMed: 10747206]
34. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. *J Urol* 2006;175:1138–1142. [PubMed: 16469640]
35. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. *J Cell Sci* 2007;120:2864–2874. [PubMed: 17666428]
36. Porreca F, Burgess SE, Gardell LR, Vanderah TW, Malan TP Jr, Ossipov MH, et al. Inhibition of neuropathic pain by selective ablation of brainstem medullary cells expressing the mu-opioid receptor. *J Neurosci* 2001;21:5281–5288. [PubMed: 11438603]

37. Ossipov MH, Hong Sun T, Malan P, Lai J, Porreca F. Mediation of spinal nerve injury induced tactile allodynia by descending facilitatory pathways in the dorsolateral funiculus in rats. *Neurosci Lett* 2000;290:129–132. [PubMed: 10936694]
38. Ledeboer A, Sloane EM, Milligan ED, Frank MG, Mahony JH, Maier SF, Watkins LR. Minocycline attenuates mechanical allodynia and proinflammatory cytokine expression in rat models of pain facilitation. *Pain* 2005;115:71–83. [PubMed: 15836971]
39. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* 2005;103:813–820. [PubMed: 16192774]
40. De Kock M, Lavand'homme P, Waterloos H. The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. *Anesth Analg* 2005;101:566–572. [PubMed: 16037177]
41. Senturk M, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalcin S, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2002;94:11–15. [PubMed: 11772793]