LETTER TO THE EDITOR

Thoracic Outlet Syndrome as a Disorder of Neurogenic Inflammation

To the Editor:

The management of neurogenic thoracic outlet syndrome (TOS) continues to be controversial. Its variable symptomatology, the paucity of "objective" clinical findings, together with its varied and often intermittent course, may be confusing and is viewed with skepticism by many physicians.[1] The lack of a clearly defined, effective medical treatment strategy is a major factor in the progression of symptoms and ensuing disability in affected patients. The pathophysiology of this disorder remains undefined. Symptom onset commonly follows single-force cervical flexion/extension (whiplash) injury or repetitive trauma associated with poor upper extremity positioning in the work place. Related predisposing factors in this predominantly female population in their third and fourth decades include musculoskeletal abnormalities, fibrous bands, and posttraumatic malpositioning of the plexus roots in the scalene triangle. However, the presence of these same factors observed in normal individuals during routine autopsy, and the absence of clinical symptoms in numerous individuals who have experienced similar traumatic events are not easily reconciled and underscore their insufficiency as explanations. Achieving an accurate diagnosis combined with a better understanding of the disease mechanisms is important given the growing incidence of individuals experiencing hand, shoulder, and arm pain and paresthesias referable to the brachial plexus.

On the basis of my personal evaluation and treatment of more than 1,500 patients exhibiting brachial plexus irritability, I propose the following hypothesis as a pathophysiological mechanism(s) involved in neurogenic TOS. The brachial plexus roots, following related trauma, develop a neurogenically induced inflammation and innervated fibrosis, which provide a cytokine-based mechanism for continued, repetitive neural inflammation without demyelinization or frank neuronal death. This would explain the lack of findings on electrodiagnosis or imaging modalities given the small size of the fibrotic lesions.

The typical time course of symptom formation is instructive. Distal paresthesias usually begin to occur following prolonged repetitive work with the upper limbs outstretched. Paresthesias are paradigmatic for neural ischemia. Aching pain follows with increasing use of the upper limb(s) or as a result of contusive injury, improving with rest. As the upper extremities, shoulders, and neck continue being used in ways that increase traction on the trunks of the brachial plexus, symptoms begin to increase over time and take longer to improve with rest. At some point, often 3 to 6 months after their initial appearance, symptoms become constant. This course argues for the increasing sensitization of the nerves involved. Sensitization of the nerves is further evidenced by the spread of symptoms. Swelling in the dorsi of the hands, as well as supraclavicularly becomes a common occurrence. Pain analogous to that of "sympathetically mediated disorders," namely, burning and lancing pains with areas of hyperesthesia and hypoesthesia, makes its appearance. Intermittent motor weakness becomes a frequent accompaniment of these increasing symptoms, as does symmetrical, contralateral involvement. The symptom complex is not mononeural or restricted to myotomes or dermatomes, although typically there is preponderance of ulnar nerve involvement. Within a year or so of symptom onset, the clinical presentation commonly progresses to involve all 3 brachial plexus trunks. Double and triple crush injuries become common. Mirror symptoms follow. This spread also activates the cervical plexus (paravertebral neck pain), the greater occipital nerves (radiating headaches), and often vagal (GI

The Editors invite readers to submit letters commenting on the contents of articles that appear in the Journal. Also welcome are brief communications in letter form reporting investigative or clinical observations without extensive documentation and with brief bibliography (five titles or less), not requiring peer review but open to critique by readers. Letters to the Editors should be no more than 500 words in length and they may have to be edited for publication.

symptoms) and recurrent laryngeal (hoarseness) nerves. Raynaud's phenomenon frequently occurs with exposure to temperature extremes, implying the involvement of sympathetic and nocifensive C-fibers.

Another important observation that needs explanation is the highly variable time course for symptom progression and its intensity. Pain severity can increase in seconds with abrupt upper limb abduction or last for hours following 5 minutes of writing. This argues for a time differential release or induction of algesic compounds. This symptom sequence, whether initiated by either of the principal traumatic mechanisms, repetitive injury or direct trauma, implies a process that, over time, sensitizes nerves adjacent to the brachial plexus and, ultimately, the central nervous system (CNS).

The direct observation of the scalene triangle and its contents, exposed during supraclavicular decompression procedures, helps clarify this confusing panorama. Fibrous bands and persistent adhesions are visualized that limit the normal movement of the plexus and impose deformation and swelling, adhering it to adjacent structures.[1] Most important, in terms of the pathophysiology and continued symptom formation, is the occurrence of richly innervated small (<1 cm sq) perineural adhesions, which, as noted, are difficult to image. Careful resection of these perineural adhesions results in the normalization of blood flow in the appropriate dermatomes with resolution of the distal vasospasm as confirmed thermographically. The relief of these symptoms and signs of vasospasm following neurolysis implies that they originated from the relevant plexus roots.

In more than 100 cases utilizing intraoperative thermography, decompressive surgery documented the presence of both directly mechanical (fibrous bands, fibrotically transformed muscle, adhesions) and neurogenic (small perineural adhesions) mechanisms for neural constriction, inflammation, and distal vasospasm. Substance P (SubP) and calcitonin gene-related peptide (CGRP), present in the resected perineural adhesions as substantiated by histologic immunoassay, provide the basis for continued neurogenic inflammation.[2] Reoperation underscores the relevance of these observations by the presence of exuberant recurrent perineural fibrosis. Evidence from similar disorders in ulnar and median nerve entrapments provides corroborating support for the primacy of fibrosis in initiating and continuing symptomatology in these disorders. Surgical decompressions of the ulnar and median nerves in the elbow, forearm, wrist, and hand all note the presence of significant fibrosis, occurring both perineurally and endoneurally. Endoneural fibrosis was felt to be most damaging because of its primary appearance and more direct effect on nerves and blood vessels.[3]

Based on my intraoperative observations of highly innervated perineural fibrosis secreting inflammatory factors, it is highly likely that the endoneural fibrosis is similarly innervated. Neuropeptides expressed by this innervated fibrosis are well recognized as important mast cell activators. Mast cells reside in significant numbers endoneurally, clustering at C-fiber convolutions, synaptic junctions of the nervi nervorum, and perivascularly about the vasa nervorum. Their activation is biphasic with either explosive extrusion of granules, which can volume increase by a factor of 1,000 in milliseconds, or by a slow tonic release lasting hours to days.[4] Messengers include vasoactive substances, glycosaminoglycans, proteases, leukotrienes, prostaglandins, interleukins, and cytokines, the most important being tumor necrosis factor (TNF) alpha and tryptases, which initiate fibroblast proliferation and collagen deposition.[5]

These mast cell mediators, coupled with the direct effect of neuropeptides in the vasa nervorum produce loosening of endothelial junctions, edema, and recruitment of lymphocytes and monocytes.[6] The result is a localized compartment syndrome inside the relatively rigid perineurium. The tortuous arrangement of fascicles in peripheral nerves embedded in a fibrous matrix of resident mast cells, macrophages, Schwann cells, and perineural cells is made to order for the mechanical propagation of this neurogenically induced local compartment syndrome. Symptom occurrence, as well as fibroblast proliferation and fibrosis follow.

Fibrosis spreading perineurally with reinjury fixes the nerve, and focally increases the mechanical strain on the nerve, causing vasospasm of the vasa nervorum.[7] Delayed symptom occurrence could be explained by the slow tonic release of vasospastic mast cell mediators noted above. In and of itself, this facilitates the creation of intermittent symptoms, much like a pressure cuff. What is more worrisome, and certainly more debilitating over time, is the consequent proliferative response, which worsens symptoms, facilitates the ease with which they arise, and lengthens any recuperative processes. The originally neurogenic-induced localized inflammation begins to spread both endoneurally and perineural-

ly, most likely via cytokine-mediated mechanisms promoting adhesions, their innervation, and, ultimately, the activation of the CNS. Neural ischemia gives rise to yet another dimension of injury: ischemia-reperfusion, which has been shown to produce entrapment symptomatology even with minimal ischemia as long as it is repetitive.[8] This could augment and consolidate the above-cited tissue changes.

Pharmacologic manipulations corroborate the primacy of neurogenic inflammation in TOS. Mu receptor agonists are minimally effective in controlling the chronic pain of TOS, producing a generalized numbness, but little amelioration of the more intense symptoms. This is characteristic of neuropathic/neurogenic disorders. Interestingly, nalbuphine, a kappa and sigma agonist, is consistently more effective and has minimal side effects. Octreotide, a somatostatin analog that quickly down-regulates neuropeptide production (SubP, CGRP, vasoactive intestinal peptide (VIP), etc), is effective during early flare-ups, corroborating the importance of neurogenic peptides in initiating symptoms.[9] Octreotide-labeled positron emission tomography is a potential diagnostic method because of its ability to image localized neurogenic inflammation. Topical nitroglycerin can lessen pain significantly, more so than opiates. This points to the importance of endothelial factors that are nitric oxide mediated as well as the importance of vascular integrity. Antiinflammatory agents modulating cyclooxygenases show little symptomatic benefit, possibly quieting the effects of direct mechanical irritation. Substantiating the importance of TNF-alpha, a major cytokine of mast cells, Etanercept, a TNF-alpha blocker, eliminates the diffuse and spreading pain accompanying flare-ups.

Also noteworthy is the observation that low-dose heparin can produce symptoms relief; lasting weeks to months. Heparin is a complicated mix of glycose aminoglycans with pleiotropic functions. Only 3% of the heparin functional sites are dedicated to anticoagulation. The rest regulate the extracellular matrix, cytokines, chemokines, and growth factors; normalize the endothelium, leukocyte migration, and cellular junctions; and stabilize mast cells. Its tissue half-life in the extracellular matrix is on the order of several weeks. Heparin has been shown to reduce postradiation neuropathy, inflammation, and pain in severe burns, asthmatic bronchoconstriction, the symptoms of irritable bowel syndrome, and the pain of nerve entrapments by direct action on peripheral nerves and their extracellular matrix.[4] Stretch and micromovement activate nervi nervorum to discharge inflammatory neuropeptides with consequent vasospasm, bleb formation, and ischemia.

These neuropeptides (SubP, CGRF, and others) can also produce sudden mast cell degranulation with acute symptoms, or, alternatively, a more gradual release, increasing symptomatology over time and explaining the clinically observed time-variable symptom formation. These cytokines and vasoactive compounds, released by mast cells and nervi nervorum (primarily nocifensive C-fibers), result in increased neural irritability and sensitivity, progressively involving the local microvasculature with increased vasospasm and initiating endothelial dysjunction, edema, and leukocyte and macrophage migration with a resulting endoneural compartment syndrome. Fibroblast and mast cell migration follow, as does growth factor (NGF, brain derived neurotrophic factor, fibroblast growth factor, etc)-induced innervated fibrosis. Reinjury occurs easily in these sensitized nerves , the fibrosis spreads, resulting in a vicious cycle of progressive neuronal activation, edema, stasis, and more extensive, innervated fibrosis. Given the relatively rigid perineurium, and the sinuous and interdigitating course of the fascicles, a compartment syndrome results. Continued cytokine elaboration is sufficient to evoke symptom spread, the establishment of double or triple crush injuries, and CNS sensitization, as well as the appearance of a mirror syndrome. Kindling, hypoesthesia/hyperesthesia, allodynia, and Raynaud's phenomenon follow.

Direct trauma (excessive flexion/extension and seat belt contusions during motor-vehicle accidents, clavicular fractures, thrombi, or aneurysms) to the thoracic inlet structures can also initiate an inflammatory response and allow the above-described perturbations to occur. Neurogenically induced perineural inflammation could result in scalene muscle fibrosis and transformation and initiate or enhance the pathological effect of existing interdigitations or fibrous bands. The etiologic explanation for TOS caused by volume increase in the scalene triangle and consequent compression of the trunks of the plexus is insufficient to account for the late onset of symptoms and the consequent progression and manifestations of spreading symptoms. Direct irritation of the plexus is certainly important, but alone it is not sufficient.

Neurogenic inflammation, with its cascade of swelling, cellular recruitment, and fibrosis, provides a more nearly comprehensive explanation. This description of pathological events and their

consequences explains much of the often cryptic initiation and clinical progression of neurogenic TOS. The spread of innervated fibrosis with continued reinjury presents a mechanism for increasing symptoms, the involvement of sympathetic and motor nerves, as well as distal, proximal, and adjacent neural sensitization. This hypothesis allows for greater diagnostic and clinical clarity and redefines the direction of treatment. Administration of long-term mast cell-stabilizing agents, cytokine and neuropeptides inhibitors, and endothelium-stabilizing agents may offer the hope of "effective" medical treatment for this disabling condition.

Wladislaw Ellis, MD
2445 Carleton St.
Berkeley, CA 94704
E-mail: w_ellis@sbcglobal.net

REFERENCES

1. Cheng S, Ellis W, Stoney R: Thoracic outlet syndrome: Supraclavicular approach. In Vascular Surgery, ed. 5, ed. by Jamieson C, Yao J. London: Chapman and Hall, 1994, pp 475-482.
2. Ellis W, Cheng S: Intraoperative thermographic monitoring during thoracic outlet decompressive surgery. Vasc Endovasc Surg 37:253-257, 2004.
3. Rosenbaum R, Ochoa J: Acute and chronic mechanical nerve injury: Pathologic, physiologic, and clinical correlations. In: Carpal Tunnel Syndrome and Other Disorders of the Median Nerve. Boston: Butterworth-Heinemann, 1993, pp 197-230.
4. Ellis W: Heparin alleviates pain in nerve entrapments. AJPM 13:54-59, 2003.
5. Dines K, Powell H: Mast cell interactions with nervous system; relationship to mechanisms of disease. J Neuropathol Exp Neurol 56:627-640, 1997.
6. Richardson J, Vasko M: Cellular mechanisms of neurogenic inflammation. Pharm Exper Ther 302:839-825, 2002.
7. Greening J, Smart S, Leary R, et al: Reduced movement of median nerve in carpal tunnel during wrist flexion in patients with non-specific arm pain. Lancet 354:217-218, 1999.
8. Suo V, Freeland A: Biochemistry of carpal tunnel syndrome. Microsurgery 2004, Oct 12 [e-pub ahead of print].
9. Ellis W: Octreotide, a small peptide, alleviates burning pain and hyperesthesia: A preliminary study. The Pain Clinic 3:239-242, 1990.