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Entrapment Neuropathies: Challenging Common Beliefs With Novel Evidence

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Entrapment neuropathies are the most prevalent type of peripheral neuropathy and often a challenge to diagnose and treat. To a large extent, our current knowledge is based on empirical concepts and early (often biomechanical) studies. This Viewpoint will challenge some of the current beliefs with recent advances in both basic and clinical neurosciences.

Extradermatomal/Extraterritorial Symptoms Are Common in Entrapment Neuropathies

Classical textbooks describe that symptoms in patients with entrapment neuropathies follow defined anatomical distributions (eg, dermatome, peripheral innervation territory). However, up to two thirds of patients present with symptoms that do not correlate with defined distributions.[10,27] This may be explained by the large variability and significant overlap of dermatomes/innervation territories, as well as by symptoms originating from deeper structures (eg, myotomes, sclerotomes), which may not coincide with superficial innervation territories. These mechanisms, however, cannot account for extensive spread of symptoms as described by many patients. For instance, patients with carpal tunnel syndrome (CTS) often report symptoms in a glove distribution, as well as proximal spread into the arm.[29]

Recent data suggest a contribution of remote immune-inflammatory mechanisms to extraterritorial symptom spread. In our experimental model, mild chronic sciatic nerve compression induced an immune-inflammatory response at the level of the dorsal root ganglia, far away from the site of the sciatic nerve lesion.[37] It is well established that neurons lower their firing threshold if exposed to an inflammatory environment, leading to neuropathic pain behavior.[46] Because the dorsal root ganglia contain thousands of neuronal cell bodies originating from sites distant to the original injury, a general decrease in firing threshold can explain the spread of symptoms outside the territory of the affected nerve.

In addition, severe nerve injuries may induce a neuroinflammatory reaction with activation of glial cells at the level of the spinal cord[21] or higher pain centers.[26] This immune-inflammatory response may spread to contralateral dorsal root ganglia or dorsal horns of the spinal cord,[20] which may account for mirror pain. It could be speculated that bilateral carpal tunnel symptoms, which often disappear following unilateral surgery,[51] may be attributed to such contralateral immune-inflammatory mechanisms.

In summary, symptoms that do not follow a clearly defined dermatomal/peripheral innervation pattern do not rule out an entrapment neuropathy. Rather, extraterritorial spread occurs in the majority of patients.[10,27]

Reliance on Large-Fiber Tests Is Insufficient to Diagnose Patients With Entrapment Neuropathies

The core sign of neural damage is loss of function, which can be examined with a standard clinical neurological examination (light touch, reflexes, muscle strength) and electrodiagnostic studies.

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Abnormalities in these tests are often considered as the gold standard for diagnosing entrapment neuropathies. However, these tests may be normal in some patients (eg, approximately 25% of patients with CTS), even though the reported symptoms are strongly indicative of a neural involvement.[50]

To understand this discrepancy, it is important to remember that the abovementioned clinical neurological and electrodiagnostic tests exclusively examine large myelinated fibers (eg, A-β and motor fibers), which only make up approximately 20% of a peripheral nerve. This clinical reliance on large fiber tests stems from early animal experiments demonstrating that acute and severe nerve injuries predominantly cause degeneration of the large fiber population,[2] whereas unmyelinated fiber conduction seems relatively resistant to acute nerve compression.[12] Recent work looking at slowly progressive, mild nerve compression, which more closely mimics entrapment neuropathies, suggests that there is preferential degeneration of small fibers, whereas myelinated axons show signs of demyelination but remain largely intact.[37] Data in patients with entrapment neuropathies have confirmed that early small fiber degeneration (evidenced by reduced innervation density in skin biopsies) and dysfunction (eg, altered thermal detection thresholds) precede changes in large fiber function.[35,43] These findings suggest that relying solely on large fiber tests in clinical practice may not be sufficient to assess patients with suspected entrapment neuropathies.

Clinically, the function of small sensory fibers can be tested with quantitative sensory testing using thermal thresholds or the ability to perceive sharp pinprick sensations. There is growing evidence that small fiber dysfunction is common in patients with both distal (eg, CTS) and proximal (eg, radiculopathies) entrapment neuropathies.[39,45] Though quantitative sensory testing has the advantage of determining thresholds in a validated and standardized manner, the equipment can be too costly for clinical settings. The use of a cluster of simple clinical tests, such as neurotips for pinprick sensation and warm and cold coins for thermal thresholds, may be an inexpensive and valid option for diagnosing small fiber degeneration.[31]

Value and Pitfalls of Neurodynamic Tests

Neurodynamic tests were first described in the late 19th century[42] and introduced into physiotherapeutic practice following the pioneering work of Bob Elvey, David Butler, and Michael Shacklock. The original terms, such as *brachial plexus tension test*, *upper-limb tension test*, and *adverse mechanical tension*, suggest that the underlying neural disorders were due to abnormal tension. However, this view has changed over time, in that the tests are not tests of tension but, rather, examine neural mechanosensitivity. Thus, the nomenclature was adjusted to *neural tissue provocation tests* or *neurodynamic tests*. Unfortunately, the nomenclature is still not used uniformly, leading to misconceptions in the medical field.

Neurodynamic tests are part of a standard clinical examination, but the interpretation of these tests and what constitutes a positive test vary greatly in the literature. While some define a positive response as the reproduction of the patient's symptoms together with reduced range of motion in the symptomatic limb compared to the asymptomatic side, it has recently been suggested that partial reproduction of symptoms and structural differentiation are essential criteria for a positive test.[28] Certainly, sensitizing maneuvers are crucial for differentiating nerve-related mechanosensitivity from other soft tissue–related mechanosensitivities. Furthermore, pain responses to specific neurodynamic tests should correlate with pain responses on respective active limb movements,[19] as both movements induce strain and excursion of the affected nerve structure.

The interpretation of neurodynamic tests can be challenging. Historically, neurodynamic tests were thought to be diagnostic for entrapment neuropathies and are still frequently used for this purpose in clinical and research settings. An increasing body of literature suggests, however, that these tests in isolation have limited diagnostic performance.[49] Indeed, a significant percentage of patients with confirmed entrapment neuropathies present with negative neurodynamic tests.[3] The explanation for this phenomenon is that neurodynamic tests are tools to assess gain of function, that is, hypersensitivity to a mechanical stimulus, and do not assess loss of function, which is the predominant feature in some patients with entrapment neuropathies.[35,45] Of note, recent studies suggest that those patients with more severe loss of nerve fiber function are less likely to show signs of heightened nerve mechanosensitivity.[3,8] These findings indicate that negative neurodynamic tests do not exclude the presence of nerve dysfunction. It is also important to note that exaggerated responses on neurodynamic testing do not necessarily imply sensitization of peripheral nervous tissues, but can be attributed to widespread or generalized hypersensitivity, as demonstrated by bilateral pain responses on neurodynamic testing in patients with whiplash-associated disorders[41] and fibromyalgia.[44] Therefore, test responses should always be interpreted within the framework of a comprehensive clinical examination and sound reasoning. The skillful use of tests for heightened nerve mechanosensitivity and their careful interpretation remain important, as targeted treatment can improve patient outcome.[34]

Another misconception is that signs of heightened nerve mechanosensitivity imply the presence of neuropathic pain. Under the former definition of neuropathic pain, that is, "pain caused by a primary lesion or dysfunction of the nervous system," one could interpret noncompliance to movement as a dysfunction of the nervous system. However, the new definition, "pain caused by a lesion or disease of the somatosensory system,"[22]

refers to the presence of nerve damage. Numerous experimental and clinical studies[1,7,14,48] have demonstrated that features of heightened nerve mechanosensitivity can be present in the absence of any nerve damage, hence in the absence of neuropathic pain. In this case, the underlying pain is classified as nociceptive pain,[24] which is possibly initiated by activation of nociceptors within the connective tissue of the peripheral nerve (nervi nervorum). However, heightened neural mechanosensitivity can also coexist with signs of nerve damage and associated neuropathic pain.[45]

Neurodynamic Treatments: Beyond Biomechanical Effects

Neurodynamic treatments are commonly used in the management of entrapment neuropathies, with proven benefits for nerve-related neck/arm and back/leg pain.[4] The rationale behind neurodynamic treatments has largely been based on biomechanical principles. Indeed, several cadaver and in vivo studies support the notion that neurodynamic techniques, and "sliders" in particular, are capable of inducing longitudinal movement of neural tissues in relation to their surrounding structures.[11] This biomechanical effect seems to be desirable to address the reduced nerve excursion that is observed in patients with CTS.[15] However, similar reductions in nerve excursion in other entrapment neuropathies have either not been studied or not been confirmed.[30] To our knowledge, no study to date reports changes in nerve gliding following neurodynamic interventions in patients with entrapment neuropathies. Of note, though carpal tunnel surgery does not alter neural excursion, symptoms subside.[47] One could thus argue that biomechanical factors are unlikely to account for symptoms and, therefore, may not be the main targets of nonsurgical management.

Recent advances in neuroscience have suggested potent neurophysiological effects of neurodynamic treatments. These treatments can induce immediate (but mostly short-lasting) hypoalgesia in humans,[5,6] and may contribute to the dispersal of intraneural edema.[9,18,38] Animal studies revealed that neural mobilization may induce anti-inflammatory effects beyond the lesion site, including within the dorsal root ganglia[33] and higher pain centers.[17] Furthermore, these techniques may activate endogenous opioid analgesic pathways in the midbrain[32] and facilitate peripheral nerve regeneration.[13] These experimental data supporting neurophysiological effects are encouraging, but further research is required to confirm these findings and to establish potential dose-dependent effects of neural mobilizations.

Management: Treating Peripheral or Central Mechanisms?

In patients with entrapment neuropathies, as in many other musculoskeletal conditions, the contribution of central mechanisms has gained increasing interest in the past decade. Indeed, patients show signs of widespread hyperalgesia,[16,52] altered conditioned pain modulation,[40] as well as structural and functional (sub)cortical changes.[23,36] These findings are suggestive of central mechanisms, such as central sensitization, changes in descending inhibition/facilitation, or remote neuroinflammation.

Central sensitization is thought to be the cause of persistent pain where peripheral triggers are absent (or not detectable with our current medical technology). In patients with entrapment neuropathies, however, peripheral afferent barrage continues to be abnormal (too much and/or too little), which will undeniably perpetuate central adaptations. The importance of the peripheral trigger in entrapment neuropathies is well established: there is often immediate relief of focal and widespread symptoms following decompression surgery or steroid injections,[25] even after long-standing symptoms. These findings highlight that the treatment of the peripheral trigger—if identifiable and responsive to management—is crucial, even when patients show signs of central contributions. Nevertheless, the scientific evidence for nonsurgical management to address the peripheral and central mechanisms in patients with entrapment neuropathies remains sparse, and future research is required to evaluate the most effective treatment strategies.

Take-Home Message

In light of the emerging evidence, we recommend that clinicians consider the following when assessing and treating patients with entrapment neuropathies:

- Nondermatomal/territorial distribution of symptoms is the norm and not the exception, and certainly does not exclude the presence of an entrapment neuropathy
- Specific tests for the small fiber population should be included in the standard clinical neurological examination
- Neurodynamic tests are not diagnostic for entrapment neuropathies, but detect heightened neural mechanosensitivity
- Negative neurodynamic tests do not exclude nerve dysfunction
- Signs of heightened nerve mechanosensitivity do not imply the presence of neuropathic pain
- The effects of neurodynamic treatment may extend well beyond biomechanical mechanisms
- Treatment of the peripheral trigger, if identifiable and responsive to treatment, remains an integral part of management, even when central mechanisms are present

The scientific evidence surrounding neural pathology has increased exponentially over the past decade, and future research will further challenge our understanding of entrapment neuropathies. Undoubtedly, a comprehensive scientific approach, including both basic as well as clinical studies, is required to improve our understanding of the pathomechanisms, assessment tools and their interpretation, as well as optimal management options for patients with entrapment neuropathies. ◉

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