PATHOPHYSIOLOGY

Neuropathic pain syndromes represent a heterogeneous group of conditions, and as a result, one mechanism or etiology cannot explain the underlying pathology. Changes may occur in the peripheral, central, and autonomic nervous system, and each can contribute to the development of chronic neuropathic pain. In fact, multiple mechanisms may be involved in most neuropathies.

In the peripheral nervous system, numerous mechanisms have been proposed to explain the generation of neuropathic pain.[3,4] These mechanisms include abnormal nociceptor sensitization and ectopic impulse generation. For example, after nerve injury, regenerating axons discharge spontaneously and the threshold to various noxious stimuli is lowered. Thus, the neuron becomes more sensitive to any stimulation, leading to spontaneous pain and hyperalgesia. Another proposed peripheral mechanism for neuropathic pain is the increased sensitivity of afferent neurons to sympathetic nervous system activation and noradrenergic agonist receptor binding. Furthermore, neuropeptides such as the cytokine tumor necrosis factor-α are released in response to inflammation, specifically macrophage activation. These cytokines are believed to generate spontaneous ectopic activation of nociceptors. Other hypothesized peripheral mechanisms include the development of ephaptic conduction between sensory neurons, where electrical currents in one neuron excite impulse activity in nearby neurons. Alterations in ion channel expression also have been proposed, specifically down regulations of Na+ channels and loss of N-type Ca+ channels.

Central nervous system changes may contribute to the development of neuropathic pain. In the spinal cord neuropathic pain is associated with central sensitization of nociceptive neurons.[5,6] Central sensitization refers to changes in the primary afferent and spinal neurons that alter nociceptive responses. One such altered response is hyperalgesia, where the patient will describe severe pain to a stimulus that in most situations is only mildly painful (e.g., pinprick). Central sensitization is mediated, in part, through neuropeptides, such as substance P, and excitatory amino acids that activate the NMDA receptor, including glutamate. Reorganization of primary afferent input with lamina II (substantia gelatinosa) of the dorsal horn of the spinal cord may also contribute to the central mechanisms of neuropathic pain. As peripheral nerve damage occurs, C-fiber terminals within lamina II degenerate. The resulting vacancy allows sprouting of A–β-mechanoreceptors into lamina II, creating the opportunity for innocuous stimuli such as touch to activate central nociceptors. The clinical outcome of this process may be tactile allodynia, often seen in neuropathic pain states. Decreased inhibitory pain pathways, including decreased levels of GABA receptors in the spinal cord and decreased blood and CSF levels of adenosine may also add to the phenomenon of neuropathic pain.[7,8] More recently, cortical changes have been described as a consequence of chronic pain.[9] Greater understanding of the peripheral and central mechanisms of neuropathic pain will one day lead to improved therapeutic options.

COMMON NEUROPATHIC PAIN SYNDROMES

Painful neuropathies may arise from a variety of conditions, including disease related and treatment associated etiologies.[10-12] Common neuropathies are listed in Table 1.

ASSESSMENT

The diagnosis of neuropathy begins with an extensive history and continues with a comprehensive physical examination.[13] Ancillary diagnostic tests may be indicated in some circumstances.

History

During the history, patients often use terms such as "burning", "tingling", "electrical", "stabbing", or "pins and needles" to describe neuropathic pain. They may describe tactile allodynia or pain as a result of light touch. A common complaint is the inability to