Differential Diagnosis: Nociceptive and Neuropathic Pain

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Abstract

Pain, both acute and chronic, affects millions of people in the United States. Pain can be categorized along a variety of dimensions, including one of the most important divisions, nociceptive versus neuropathic pain (NP). Nociceptive pain results from activity in neural pathways secondary to actual tissue damage or potentially tissue-damaging stimuli. NP is chronic pain that is initiated by nervous system lesions or dysfunction and can be maintained by a number of different mechanisms. Three common conditions that are often associated with acute and chronic NP are painful diabetic peripheral neuropathy (DPN), painful postherpetic neuralgia (PHN), and cancer. Although estimates of DPN vary widely depending on the assessment criteria employed, as many as 50% of people with diabetes have some degree of DPN. PHN develops secondary to herpes zoster infection, and there are 600 000 to 800 000 cases of herpes zoster in the United States each year, with 9% to 24% of patients progressing to PHN. Acute or chronic NP may occur in more than 50% of patients with cancer pain. Patients with painful DPN, PHN, or cancer may present with a variety of acute or chronic NP symptoms, and it is important to distinguish these conditions from other pain syndromes so that appropriate therapy can be initiated.

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The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] This definition recognizes pain as a subjective experience with both psychologic and sensory components. It also recognizes that tissue damage does not need to be present for pain to be experienced.

Pain has been categorized in a variety of different ways, and one division that has been particularly useful is nociceptive pain versus neuropathic pain (NP). Nociceptive pain results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli. Examples of nociceptive pain include pain after surgery, arthritis pain, mechanical low back pain, and pain associated with sports injuries.[2,3] In contrast, NP is chronic pain that is initiated by nervous system lesions or dysfunction and can be maintained by a number of different mechanisms. For example, excess stimulation of nociceptive pathways or damage to inhibitory pathways can alter the balance between painful and nonpainful sensory inputs so that pain results in the absence of nociceptor stimulation.[2,4,5] Thus, NP may be present without any readily demonstrable physical findings.[5]

ETIOLOGY AND PATHOBIOLOGY OF NEUROPATHIC PAIN

NP can arise from a variety of different conditions that affect the peripheral and/or central nervous systems (**Table 1**).[5] Disorders of the brain or spinal cord, such as multiple sclerosis, stroke, and spondylotic or posttraumatic myelopathy, can lead to NP. Peripheral nervous system disorders that may be involved in the development of NP include diseases of the spinal nerve roots, dorsal root ganglia, and peripheral nerves. Damage to peripheral nerves that occurs in association with amputation, radiculopathy, carpal tunnel syndrome, and other entrap-

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ment neuropathies can also give rise to NP.[4] Abnormal sympathetic nerve activation, catecholamine release, and activation of free nerve endings or neuromas can give rise to sympathetically mediated pain.[4] NP can also be associated with infectious disease, most notably human immunodeficiency virus (HIV). Cytomegalovirus, which is often present in patients with advanced HIV disease, may also cause debilitating low back pain, radicular pain, and myelopathy.[4] NP is a common and important source of morbidity in patients with cancer. Such pain in cancer patients can arise from tumor-related compression of neural tissue or nervous system injury secondary to radiation or chemotherapy.[4,6]

The clinical features of NP are summarized in **Table 2**, and a number of different pathologic processes have been suggested as factors in their development and maintenance. These include insertion of ion channels into nerve fiber membranes, alterations in receptors associated with increased levels of inflammatory cytokines, sprouting of primary afferent axon terminals in the dorsal horn of the spinal cord, cross-talk between sympathetic and somatosensory afferents, reduced numbers of gamma-aminobutyric acid-containing neurons in the spinal cord, and hyperexcitability associated with increased glutamatergic neurotransmission secondary to upregulation of metabotropic glutamate receptors in the dorsal horn.[3,4,7,8]

Table 1. Common Types of Neuropathic Pain

Peripheral neuropathic pain
Acute and chronic inflammatory demyelinating polyradiculoneuropathy
Alcoholic polyneuropathy
Chemotherapy-induced polyneuropathy
Complex regional pain syndrome
Entrapment neuropathies (eg, carpal tunnel syndrome)
HIV sensory neuropathy
Iatrogenic neuralgias (eg, postmastectomy pain or postthoractomy pain)
Idiopathic sensory neuropathy
Nerve compression or infiltration by tumor
Nutritional deficiency-related neuropathies
Painful diabetic neuropathy
Phantom limb pain
Postherpetic neuralgia
Postradiation plexopathy
Radiculopathy (cervical, thoracic, or lumbosacral)
Toxic exposure-related neuropathies
Tic douloureux (trigeminal neuralgia)
Posttraumatic neuralgias
Central neuropathic pain
Compressive myelopathy with spinal stenosis
HIV myelopathy
Multiple sclerosis–related pain
Parkinson's disease–related pain
Postischemic myelopathy
Postradiation myelopathy
Poststroke pain
Posttraumatic spinal cord injury pain
Syringomyelia

HIV indicates human immunodeficiency virus.
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DIABETIC PERIPHERAL NEUROPATHY

Prevalence, Risk Factors, and Natural History

Diabetic peripheral neuropathy (DPN) is very common. Although prevalence estimates vary widely depending on the assessment criteria employed, as many as 50% of people with diabetes have some degree of DPN.[9] The most prevalent form of DPN is distal symmetric sensorimotor polyneuropathy, which is also the most common event leading to lower limb amputation in patients with diabetes. The Rochester Diabetic Neuropathy Study reported some form of neuropathy in 60% of subjects with type 1 or type 2 diabetes, and the prevalence of polyneuropathy was 48% in this group.[10] A recent report from the GOAL A1C study group indicated that 37% of a sample of 4628 patients with type 2 diabetes had neuropathy. Given that the overall prevalence of diabetes (both type 1 and type 2) in the United States is 20.8 million,[11] these results suggest that as many as 7.7 million people in this country may have some degree of DPN.

Additional epidemiologic study results indicate that the prevalence of DPN increases with both age and duration of disease.[12]

Table 2. Features of Neuropathic Pain

May occur in the presence of a neurological deficit (stroke, brachial plexus avulsion, spinal cord injury).
May be unaccompanied by ongoing tissue damage.
May occur in an area of sensory loss.
May be burning, shooting (ie, different from nociceptive sensations), or dysaesthetic (unpleasant abnormal sensations, such as "pins and needles").
May occur spontaneously or in response to normally nonpainful stimuli (ie, allodynia).
May be greater than expected pain in response to a painful stimulus (ie, hyperalgesia) or pain that increases with a repetitive stimulus (ie, hyperpathia).

Source: Reprinted with permission from Reference 2.

Results from the Diabetes Control and Complications Trial showed further that hyperglycemia is a significant risk factor for the development of DPN in patients with type 1 diabetes. This large-scale, long-term trial demonstrated that tight glycemic control decreased the appearance of neuropathy by 69% over a mean follow-up period of 6.5 years.[13]

Although the severity of the neuropathy in DPN may fluctuate, painful symptoms tend to persist for years. Review of the natural history of the disease also suggests that DPN-associated pain tends to worsen in most patients over long-term follow-up, although severe pain can also occur early in the course of the disease.[14]

Classification of DPN

DPN can be classified as acute or chronic. Acute DPN is an uncommon transient condition that affects the lower limbs and is distressing and occasionally incapacitating. This acute condition occurs in the context of either poor glycemic control or a rapid improvement in control. Chronic DPN is defined by pain symptoms that have been present for at least 6 months.[15]

Symptoms of Painful DPN

Diabetic neuropathy has been used to describe a large number of diffuse and focal neuropathic syndromes that result from damage to peripheral somatic or autonomic nerve fibers (**Table 3**). These syndromes include distal, symmetric sensorimotor polyneuropathy, autonomic neuropathy, symmetric proximal lower limb motor neuropathy (amyotrophy), cranial neuropathy, radiculopathy/plexopathy, entrapment neuropathy, and asymmetric lower limb motor neuropathy.[16]

Distal symmetric sensorimotor polyneuropathy, the most common form of DPN, has an insidious onset. In most people, the most distal extremities (the toes) are the first part of the body to be affected. Symptoms in patients with symmetric sensorimotor polyneuropathy may be described as either negative (eg, loss of feeling) or positive (eg, burning pain or muscular weakness).[15] Loss of small unmyelinated fibers in these patients may predispose them to injury and foot ulceration.[16] Patients with DPN may also experience carpal tunnel syndrome, or meralgia paresthetica, and/or pain in the distribution of the lateral femoral cutaneous nerve. Symptoms of DPN may be exacerbated at night, and they may prevent sleep, resulting in secondary fatigue, irritability, and myofascial dysfunction.[4]

Many patients with distal symmetric sensorimotor polyneuropathy are asymptomatic in early stages of the disease, and careful physical examination and sensory testing may be necessary to detect the syndrome. In the Rochester Diabetic Neuropathy Study, about 48% of the subjects evaluated had evidence of polyneuropathy, but only 15% were symptomatic.[10] Similarly, results from 7892 patients in the GOAL A1C study indicated physician-diagnosed neuropathy in 18% of patients versus 30% who demonstrated mild-to-moderate neuropathy, and an additional 7% with severe neuropathy demonstrated by monofilament testing.[17]

Clinical diagnosis of DPN, particularly in patients with sensorimotor polyneuropathy, may be difficult, because symptoms are variable, ranging from a complete absence of pain with disease perhaps reflected only by an insensitive foot ulcer to very severe pain. Sensory symptoms and signs of DPN are more common than motor symptoms,

but the latter may include reduced ankle reflexes and/or minimal distal muscle weakness.[18]

POSTHERPETIC NEURALGIA

Herpes zoster is caused by a reactivation of the varicella zoster virus (VZV), the primary infection that causes chicken pox in children.[19] After the chicken pox infection, VZV remains dormant in sensory ganglia throughout the body. Reactivation is more common in older individuals and in those with compromised immune systems. Reactivation results in the rash commonly referred to as shingles, which is accompanied by acute pain. Pain that persists for extended intervals after the rash has subsided is postherpetic neuralgia (PHN).[19] Although definitions for PHN vary, the one set forth by the American Academy of Neurology is pain that persists for more than 3 months after resolution of the rash.[20]

The etiology of PHN is not completely understood; however, it has been shown that patients with this condition have damage to sensory nerves, dorsal root ganglia, and spinal dorsal horn.[21] It is thought that viral particles spread to these sites after reactivation, and that this is accompanied by inflammation, immune response, hemorrhage, and damage to peripheral sensory neurons and their processes.[22] It is also known that VZV infection can invade the spinal cord and central nervous system blood vessels, causing a wide range of serious neurologic symptoms.[23]

Prevalence

Review of results from epidemiologic studies indicates that there may be as many as 1 million cases of herpes zoster in the United States each year. It has also been estimated that between 9% and 24% of these patients will develop PHN.[4] The risk of PHN secondary to herpes zoster infection increases progressively with age. It has been estimated that PHN follows herpes zoster infection in 2% of people older than 40 years of age, 21% of those 40 to 60 years old, and in 40% of those older than 60.[24] Age-associated decline in immune system function explains the association between older age and greater risk of herpes zoster, although the explanation for the greater risk of PHN in older herpes zoster patients is not understood. Patients who have diseases or who are receiving treatments that compromise the immune system are also at increased risk for herpes zoster infection and PHN. It has been noted that the incidence of herpes zoster is up to 15 times higher in HIV-positive people than in those without HIV infection, and that the risk for this condition is also elevated in patients with Hodgkin's disease, non-Hodgkin's lymphoma, and leukemia, as well as those undergoing bone marrow or solid organ transplantation.[14,21]

Other factors that may increase the risk for herpes zoster infection include long-term corticosteroid use, chemotherapy, and radiation therapy.[21] Race also appears to influence the risk for herpes zoster infection. Assessment of 3206 community-dwelling people older than 64 years of age indicated that blacks had an odds ratio of 0.25 versus whites for development of herpes zoster infection.[25] Characteristics of acute infection associated with increased risk for PHN include greater severity of rash and acute pain, more severe sensory impairment in the affected dermatome, and psychologic distress.[14]

Table 3. Classification of DPN

A. Diffuse
1. Distal symmetric sensorimotor polyneuropathy
2. Autonomic neuropathy
a. Sudomotor
b. Cardiovascular
c. Gastrointestinal
d. Genitourinary
3. Symmetric proximal lower limb motor neuropathy (amyotrophy)
B. Focal
1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy (amyotrophy)

DPN indicates diabetic peripheral neuropathy.
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Symptoms of Herpes Zoster and Postherpetic Neuralgia

Acute Symptoms. Herpes zoster typical-

ly presents with a prodrome that lasts for 3 to 4 days and may include hyperesthesia, paresthesias, and/or burning dysesthesias or pruritus along the affected dermatome(s). Pain is the most common reason that patients with herpes zoster seek treatment. This pain is often described as burning or stinging and is generally unrelenting. The thoracic dermatomes are most often affected, but any dermatome can be involved. The ophthalmic division of the trigeminal nerve is the cranial nerve involved most often in patients with herpes zoster infection.[21] These acute symptoms resolve shortly after rash healing in most patients, but a large minority of patients—particularly the elderly—develop symptoms characteristic of PHN.[24]

Postherpetic Neuralgia. In most patients, the diagnosis of PHN is not difficult, because they remember their symptomatic painful rash in the affected dermatome(s). Skin color changes and scarring may also assist in the diagnosis. There is no simple diagnostic test for PHN, and patients with this condition are identified on the basis of their clinical presentation and exclusion of other disease processes that may mimic PHN.[22]

Patients with PHN may present with a wide range of NP symptoms. These include ongoing pain that may be independent of any apparent external stimulus, which patients may notice more often at night or when their attention is not focused on some other activity. Patients with PHN are also likely to experience pain in response to light touch, even by their clothing (ie, allodynia). Some patients with PHN may also complain of lancinating pain (brief jolts of severe pain). Motor and autonomic symptoms are rare in PHN, but patients can occasionally present with pleural or bone pain, or a neurogenic bladder or rectum after a herpes zoster infection.[26]

It has been suggested that patients who develop PHN fall into 3 subtypes: (1) an "irritable nociceptor" group with minimal deafferentation and touch-evoked allodynia due to peripheral nociceptor input; (2) a deafferentation group with marked sensory loss and no allodynia; and (3) a deafferentation group with sensory loss and allodynia due to central reorganization.[27] Patients with different PHN subtypes may respond differently to therapy for NP. For example, those with allodynic PHN have been predicted to receive the greatest benefit for local anesthesia, whereas this treatment may be less effective in the deafferentation group.[27]

CANCER-ASSOCIATED ACUTE AND CHRONIC NP

Acute and chronic NP are common in patients with cancer. Results from an evaluation of 593 cancer patients treated by a pain service following World Health Organization guidelines for relief of cancer pain indicated that 380 patients presented with nociceptive pain, 32 presented with acute or chronic NP, and 181 presented with mixed (nociceptive and neuropathic) pain.[28] Similarly, results from 187 consecutive patients with cancer and pain indicated that 55% had acute or chronic NP. The most frequent sites of neurologic injury were spinal nerves and the spinal cord, the cauda equina, the brachial and lumbosacral plexus, and peripheral nerves. In 93 of these patients, the pain was caused by ongoing neural injury; whereas, in 10 patients, the neural injury was long-standing and stable.[29]

Although it is clear that both cancer and its treatment can cause acute and chronic NP, the etiology of this pain is still not fully understood. However, results from recent studies of animal models of specific tumors have increased our insight into cancer-related acute and chronic NP.[30] In this model, intramedullary injection and containment of osteolytic sarcoma cells into the mouse femur result in bone destruction and pain behavior similar to that of patients with bone cancer pain. The pain in the mouse model is associated with neurochemical reorganization of sensory neurons that innervate the tumor-bearing bone and in the spinal cord segments innervated by primary afferents supplying the cancerous bone. Most recently, it has been demonstrated that an antibody to nerve growth factor can decrease this pain and reduce the peripheral and central reorganization associated with it.[31,32]

Diagnosis of acute and chronic NP in the cancer patient is generally similar to that of

other patients with pain. A prospective, cross-sectional, international, multicenter survey study carried out by the International Association for the Study of Pain Task Force on Cancer Pain has provided a comprehensive picture of pain in the cancer patient. Results from 1095 patients with severe cancer pain indicated that 92.5% had pain attributable to their cancer and 20.8% had treatment-associated pain. The average duration of pain in these patients was 5.9 months. Approximately two thirds of patients reported that the worst pain intensity during the day before the survey was ≥7 on a 10-point scale. Higher pain intensity was associated with the presence of breakthrough pain, somatic pain, and acute or chronic NP. Multivariate analysis indicated that the presence of breakthrough pain and somatic pain were associated with more intense pain. Overall, 71.6% of patients in this cohort had nociceptive pain and 39.7% had acute or chronic NP.[33]

CONCLUSION

Acute or chronic NP is very common, and it is often associated with diabetes, herpes zoster infection, and cancer. DPN is a very prevalent complication of long-standing diabetes, and recent results indicate that it affects more than one third of people with diabetes. PHN occurs less often, but its prevalence increases with age, and the number of cases might be expected to increase as the population ages. Cancer and its treatment are also common causes of acute and chronic NP. Patients with each of these conditions may present with a variety of symptoms, and results from at least 1 recent study suggest that DPN is substantially underdiagnosed.[17] Careful attention to symptoms and patient history can facilitate diagnosis of both DPN and PHN.

REFERENCES

1. International Association for the Study of Pain. IASP Pain Terminology. 1994. Available at: http://www.iasp-pain.org/terms-p.html. Accessed May 3, 2006.

2. Goucke CR. The management of persistent pain. *Med J Aust.* 2003;178:444-447.

3. American Academy of Pain Medicine. Management of chronic pain syndromes: issues and interventions. *Pain Med.* 2005;6(suppl 1):S1-S20.

4. Chen H, Lamer TJ, Rho RH, et al. Contemporary management of neuropathic pain for the primary care physician. *Mayo Clin Proc.* 2004;79:1533-1545.

5. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003;60:1524-1534.

6. Martin LA, Hagen NA. Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies. *J Pain Symptom Manage.* 1997;14:99-117.

7. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci Lett.* 2004;361:184-187.

8. Fukuoka T, Tokunaga A, Kondo E, Miki K, Tachibana T, Noguchi K. Change in mRNAs for neuropeptides and the GABA(A) receptor in dorsal root ganglion neurons in a rat experimental neuropathic pain model. *Pain.* 1998;78:13-26.

9. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic nephropathy in the US. *Diabetes Care.* 2003;26:1790-1795.

10. Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology.* 1993;43:817-824.

11. National Diabetes Information Clearinghouse. National Diabetes Statistics. NIH Publication No. 06-3892. 2005. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#7. Accessed May 3, 2006.

12. Boulton AJ. Treatment of symptomatic diabetic neuropathy. *Diabetes Metab Res Rev.* 2003;19(suppl 1):S16-S21.

13. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977-986.

14. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain.* 2002;18:350-354.

15. Quattrini C, Tesfaye S. Understanding the impact of painful diabetic neuropathy. *Diabetes Metab Res Rev.* 2003;19(suppl 1):S2-S8.

16. Greene DA, Stevens MJ, Feldman EL. Diabetic neuropathy: scope of the syndrome. *Am J Med.* 1999;107(suppl 2B):2S-8S.

17. Herman WH, Kennedy L. Underdiagnosis of peripheral neuropathy in type 2 diabetes. *Diabetes Care.* 2005;28:1480-1481.

18. Bhadada SK, Sahay RK, Jyotsna VP, Agrawal JK. Diabetic neuropathy: current concepts. *J Indian Acad Clin Med.* 2001;2:305-318.

19. McElveen WA, Gonzalez RF. Postherpetic neuralgia. *eMedicine.* 2005. Available at: http://www.emedicine.com/neuro/topic317.htm. Accessed May 3, 2006.

20. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2004;63:959-965.

21. Stankus SJ, Dlugopolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. *Am Fam Physician.* 2000;61:2437-2444, 2447-2448.

22. Argoff CE, Katz N, Backonja M. Treatment of postherpetic neuralgia: a review of therapeutic options. *J Pain Symptom Manage.* 2004;28:396-411.

23. Gilden D. Varicella zoster virus and central nervous system syndromes. *Herpes.* 2004;11(suppl 2):89A-94A.

24. Gazewood JD, Meadows S, Halverson L. Clinical inquiries. What is the prognosis of postherpetic neuralgia? *J Fam Pract.* 2003;52:496-497.

25. Schmader K, George LK, Burchett BM, Pieper CF, Hamilton JD. Racial differences in the occurrence of herpes zoster. *J Infect Dis.* 1995;171:701-704.

26. Oaklander AL. Evidence-based treatment of herpes zoster and postherpetic neuralgia. *Pain Management Rounds.* 2004;1:1-6.

27. Rowbotham MC, Petersen KL, Fields HL. Is postherpetic neuralgia more than one disorder? *IASP Newsletter.* 1999. Available at: http://www.iasp-pain.org/TC99Fall.html. Accessed May 3, 2006.

28. Grond S, Radbruch L, Meuser T, Loick G, Sabatowski R, Lehmann KA. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. *J Pain Symptom Manage.* 1999;18:174-179.

29. Manfredi PL, Gonzales GR, Sady R, Chandler S, Payne R. Neuropathic pain in patients with cancer. *J Palliat Care.* 2003;19:115-118.

30. Mantyh PW. A mechanism based understanding of cancer pain. *Pain.* 2002;96:1-2.

31. Mantyh PW. A mechanism-based understanding of bone cancer pain. *Novartis Found Symp.* 2004;261:194-214.

32. Sevcik MA, Ghilardi JR, Peters CM, et al. Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization. *Pain.* 2005;115:128-141.

33. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain.* 1999;82:263-274.