Neural-Immune Interactions: Implications for Pain Management in Patients with Low-Back Pain and Sciatica

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Bidirectional communication between the immune system and the brain and the implications of this communication are emerging concepts in pain research. Although representing a small portion of the disc degeneration syndromes, lumbar herniated discs can cause significant symptoms that may persist even after surgical interventions. Evolving evidence demonstrates that proinflammatory cytokines are a key mediator in the process of disc degeneration as well as in the pain experienced by those afflicted with lumbar herniated discs. Activated immune cells release proinflammatory cytokines, which signal the brain through humoral and neural routes. The brain responds by altering neural activity and promoting further production of proinflammatory cytokines within the brain and spinal cord. Increased local cytokine production by disc tissue irritates spinal nerve roots, resulting in pain and functional changes in neural activity. This review of the current literature explores the importance of cytokine production within the context of lumbar disc degeneration and lumbar spine pain. Furthermore, the significance of the neural-immune interaction will be examined as it relates to pain management and to patient treatment.

Key words: *proinflammatory cytokines, nucleus pulposus, lumbar herniated disc, disc degeneration*

Back pain remains an elusive clinical problem. Low-back pain is considered one of the most widely experienced health problems in the United States and is the 2nd most frequent condition, after the common cold, for which people see a physician or lose days from work. Low-back pain and sciatica are common and debilitating conditions that produce significant burden in terms of human suffering and financial cost. It is estimated that direct medical costs associated with these conditions exceed $25 billion annually (Casey 1995). Because of physical impairment and psychological morbidity, the personal impact of low-back pain and sciatica on quality of life is immense (Turk and Gatchel 2002).

Biomechanical compression of the nerve root by a herniated disc has traditionally been considered to be the sole pathogenic factor for inducing sciatica. However, because sciatica may be present in the absence of disc herniation (Olmarker and Hause 1995; Wood and

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others 1997) and the size of herniation does not correlate with pain indices (Kawakami and others 1996, 1997), other biological mechanisms of sciatic pain are now considered plausible. Recently, molecules secreted by immune cells (i.e., cytokines) have been implicated in pain transmission, and compelling new evidence (primarily in animal models) demonstrates a role for proinflammatory cytokines in the evolution and progression of low-back pain and sciatica (Watkins and Maier 2000; Watkins and others 2003). Understanding the influences of local cytokine production and its impact on perceived pain may lead to novel approaches that can improve the quality of life among patients with disc herniation and sciatic pain.

Methodology

A literature search was performed using the Ovid search engine within the categories of nursing, medicine, biology, microbiology, and cellular biology. Manuscripts were limited to the English language but were not limited by date of publication. Review and research articles related to disc herniation in animal models and human studies were included.

Mechanisms of Disc Degeneration and Nontraumatic Herniation

Disc degeneration is the initial process leading to nontraumatic disc herniation (see Fig. 1). This theoretical pathway describes the biomechanical and biochemical events responsible for the process of disc aging, or degeneration, which ultimately leads to the experience of pain phenomena (low-back pain and sciatica). Traditionally, it has been believed that the displaced disc tissue was a by-product of the disease and not an interactive element in the disease process itself. However, the discovery of elevated levels of proinflammatory cytokines within injured disc tissue by Takahashi and colleagues (1996) led researchers to conceptualize it as a biologically active tissue. Since that time, connections between the immune system, nervous system, and pain behavior in disc injury have continued to evolve. The current understanding of the mechanisms of disc degeneration and nontraumatic herniation will be reviewed in relationship to Figure 1.

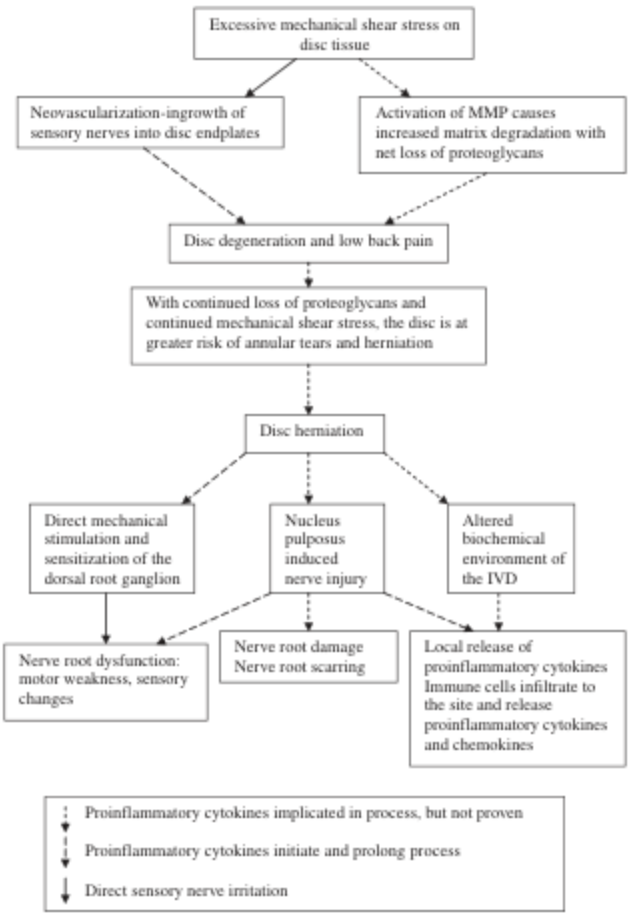

Figure 1. Mechanisms of disc degeneration and nontraumatic herniation. MMP = metalloproteinases; IVD = intervertebral disc tissue.

Mechanical Shear Stress

The function of the intervertebral disc is to provide the spine with mobility while retaining axial stability (Greenberg 2001). Although physiologic loading helps to maintain metabolism and function in intervertebral discs, excessive mechanical loading appears to be detrimental. Certain occupations pose a hazard to the rate of disc degeneration. Those occupations that entail repetitive bending, twisting, and lifting from the trunk and expose workers to whole-body vibration have a higher propensity to accelerate disc

degeneration (Bovendi 1996; Damkot and others 1984). However, Elfervig and others (2001) found other factors that influence the effect of mechanical loading on disc degeneration. In their study, treating discs with interleukin (IL)-1β, a proinflammatory cytokine known to stimulate production of metalloproteinases (MMPs), sensitized annulus cells to mechanical loading. This effect renders annulus cells more susceptible to injury from excessive load, causing the progression of disc degeneration through stimulating production of MMPs that degrade matrix, including proteoglycans. Studies have demonstrated that loss of proteoglycans is one of the main biochemical changes in the annulus of degenerative discs, making them susceptible to annulus tears and herniation (Stevens and others 1982; Benoist 2002).

Neovascularization

Nerve ingrowth into the degenerate lumbar intervertebral disc has been well documented (Palmgren and others 1996; Coppes and others 1997). Freemont and colleagues (1997) demonstrated an association between nerve ingrowth and the patient's experience of pain. These nerves had the characteristics and markers of actively growing nonmyelinated pain fibers, with substance P as the neurotransmitter. In 2002, Freemont, Watkins, Le Maitre, Baird, and others discovered that small nonmyelinated nerve fibers grow into the intervertebral disc only in areas where there is local production of the neurotrophic factor NGF. NGF is produced by microvessels, which populate the normally avascular (and aneural) intervertebral disc by extension from adjacent bone. Their study provides compelling evidence that this pattern of nerve growth and receptor expression is implicated in the innervation of painful tissues through NGF-driven axonal growth and maturation.

The stimulus that promotes microvessels to release NGF, triggering the process of nerve and vessel ingrowth, remains uncertain. However, IL-1 is currently being investigated because it is involved in cartilage homeostatis (Cawston and others 1999). IL-1 has the ability to switch chondroctyes from anabolism to catabolism, inducing cartilage breakdown at molecular and morphological levels through stimulating MMPs (van Den Berg 1999). Thus, there is growing evidence of the role of proinflammatory cytokines in matrix degradation (disc degeneration), nerve and vessel ingrowth, and pain.

There is mounting evidence that immune factors are involved not only in the initiation of disc degeneration but also in the progression of disc disease. As the injured disc tissue continues to produce elevated levels of MMPs, thereby losing proteoglycans, the diseased tissue begins to wear down. Annular tears form along the outer wall of the disc, making it more susceptible to splitting, and thus herniating, in the face of exertional forces that raise the intervertebral pressure (Benoist 2002).

When a herniated disc does occur, it produces an autoimmune inflammatory response resulting in the production of a variety of pain-producing substances. These are produced not only by infiltrating inflammatory cells but also by histiocytes, fibroblasts, endothelial cells, and chondrocytes of the disc itself. Such findings support the concept that disc-associated proinflammatory substances may be a major factor in the creation of sciatic pain. The current findings of disc herniation in animal models and human studies will be reviewed to determine how these mechanisms affect health outcomes and how they may translate into new therapies to prevent and manage the degenerated or herniated disc.

Direct Mechanical Stimulation and Sensitization of the Dorsal Root Ganglion

Dislocation of intervertebral disc tissue (IVD) by nucleus pulposus (NP) protrusion or extrusion (i.e., herniated disc) is a common source of severe pain. Herniation of the NP causes it to contact and compress the dorsal root ganglion (DRG) and spinal root that enters the spine at the vertebral level. Acute mechanical compression is sufficient to produce spontaneous activity in the sensory afferents, supporting the classic assumption that mechanical compression is the cause of pain and other neurological symptoms. Mechanical compression has been thought to account for the ischemia, edema, and demyelination that occur in the DRG and the pain that may arise from nerve endings in the outer annulus fibrosus. Olmarker and Myers

(1998) used a rat model of disc herniation to verify these hypotheses. In the 1st subset of animals, air was injected into the NP and transferred to the L_4 nerve root and DRG. The 2nd subset underwent displacement of the DRG. The 3rd subset had both disc herniation and the displacement procedure completed while the sham subset underwent exposure of the spinal canal only. Compared to animals receiving the sham protocol, the reduction in mechanical threshold was statistically significant in the combination protocol (disc herniation with DRG displacement) at days 2, 4, 16, and 18. The combination group also showed a marked reduction in the thermal latency of the left (operated) side compared to the contralateral side by 2 days postprocedure that was not normalized until 14 days postprocedure. Histologically, the nerve roots from the 1st subset demonstrated mild edema. The displacement group demonstrated more severe edema of the DRG, and the combination group demonstrated edema, endothelial and Schwann cell hypertrophy, demyelinization, and widespread myelin abnormalities at postprocedure day 21. This study demonstrated that displacement of the DRG alone (similar to mechanical compression) causes edema of the DRG and minor changes in motor function; however, with simultaneous disc herniation, there is severe cellular breakdown and significant changes in sensory function.

Pain behavior was observed by Olmarker and others (2002) using the same protocol. A single technician blindly assessed the video recordings of the rats during a 20-min interval the day after surgery, 2 weeks after surgery, and 3 weeks after surgery. In those with both disc incision and displacement, there was increased focal pain, seen as increased lifting of the hind paw on the operated side and increased rotation of the head toward the operated side, as compared with the sham group. There were no significant differences in behavior between the groups at day 14. However, 3 weeks after surgery, there was another pattern of increased immobility and decreased locomotion in the combination group as compared with the sham group. Unfortunately, the authors did not include measurements of nerve injury or proinflammatory cytokines, which would have provided insight into the biochemical and functional sequelae of mechanical stimulation and sensitization of the DRG.

NP-Induced Nerve Injury

Pathological pain can arise as a consequence of the protrusion of the NP into contact with the DRG and dorsal root. Although pressure per se has classically been considered as a major cause of pain, there is growing evidence that immune-derived substances may be involved as well. Diverse immune cells and equally diverse immune cell products are potential mediators. Of these, proinflammatory cytokines have received by far the most attention. Data to date suggest a strong case in support of proinflammatory cytokine involvement in the pain of herniated discs. The cytokines may do this by inducing expression of receptors within DRGs. Also, axonal interactions with proinflammatory cytokines could increase electrical conductivity. Each of these could then lead to painful stimuli.

Olmarker and others (1993) used autologous NP harvested from the L_{3-4} intervertebral disc in hogs and placed it epidurally, in close contact with the spinal nerve roots. The control group had fat placed in the same fashion. Electromyelogram studies were used to measure nerve velocities at 1 day (84 ± 2 control; 63 ± 9 NP), 3 days (83 ± 4 control; 45 ± 16 NP), and 7 days (76 ± 11 control; 45 ± 19 NP) postimplantation. There was a significant reduction of nerve velocities in the NP group at all time points. Histological examination of the nerve fibers exposed to NP revealed axonal swelling, increased axoplasmic density, splitting of the myelin sheaths, and swelling and attenuation of the Schwann cell cytoplasm that worsened subsequently at each time point, whereas there were no histological changes in the fat group. This study suggests the presence of a biochemical substance in the NP that causes dysfunction in the nerve root and ongoing deterioration of nerve root morphology over time.

Otani and others (1997) evaluated nerve conduction velocities (NCVs) in a dog model of disc herniation. NCV was measured in normal dogs as control. The sham group had the L_7 nerve root retracted for 10 s and replaced. The herniation group had the same procedure completed with the addition of 0.01 mL of saline injected into the center of the disc with visible leakage of NP into the spinal canal. Both groups were assessed at 1, 3, and 7 days postprocedure. The NCVs in the sham groups were stable at about 70 m/s. The NCVs in

the herniation groups started to decline at day 3 (61 ± 14 m/s) and reached a maximum reduction after 7 days (39 ± 24 m/s), which was statistically significant.

Kayama and others (1998) also demonstrated functional changes in spinal nerve roots through application of NP. In this study, harvested NP and skin were cultured for 3 weeks. Culture medium, conditioned culture medium, dead autologous fibroblasts, live autologous fibroblasts, dead autologous NP cells, and live autologous NP cells were applied to the cauda equina in the same pigs, respectively, from which the cells were harvested. One week postapplication, nerve conduction velocities were recorded. The mean nerve conduction velocities in the live fibroblasts and conditioned culture medium series were slightly lower than those in the control dead fibroblast series, but they were not significant. However, the dead and live NP cells series demonstrated a statistically significant reduction. The authors concluded that the functional changes must be induced by a membrane-related structure of the NP cells or bioactive substances, such as cytokines.

Takebayashi and colleagues (2001) surgically exposed the L_5 dorsal root in rats and implanted either autologous NP or autologous fat as an implantation control. Using electrophysiologic techniques, the spontaneous discharge rate of the L_5 DRG was measured at 30-min intervals for 6 hours after implantation. A significant increase in the spontaneous discharge rate (SDR) was continuously observed from 150 min to the end of the recording (360 min) in the animals that were implanted with autologous NP. No change in SDR was noted in the animals that received autologous fat. In addition, mechanosensitivity of the DRG was measured before application and every 2 h using calibrated nylon filaments. Six hours after application, the mechanical thresholds in the NP group remained statistically elevated from those of the fat group. This study supports the hypothesis that sciatica can result from exposure of the NP to the nerve root, which caused excitation and mechanical hypersensitivity in the DRG without mechanical compression.

Yabuki and others (1998) demonstrated more specific effects on the DRG by measuring blood flow and endoneurial fluid pressure (EFP) after application of NP. Autologous NP was harvested from the amputated tail in rats and applied to the L_5 nerve root just proximal to the DRG, whereas muscle was used in the control group. DRG blood flow was measured using a laser Doppler flowmeter before application. Blood flow in the NP group was significantly decreased (by 12% and 19%) compared to the muscle group at both 3 and 4 h postapplication. EFP was recorded with a servo-null micropipette system attached to the connective tissue membrane surrounding the DRG. There was a statistically significant increase in EFP in the NP group. Histologically, the DRG in the muscle group appeared normal, whereas in the NP group, there was edema, endothelial cell activation, and myelin disruption. The results of this study demonstrate the role of NP in initiating local change in blood flow and in the inflammatory process that characterizes disc herniation.

The relationship between blood flow and motor nerve conduction velocity was examined by Otani and others (1999). Annulus fibrosus of the L_{6-7} intervertebral disc in canine models were incised and punctured by an 18-gauge needle. NP was pushed into the epidural space near the L_7 nerve root. The sham group underwent exposure of the L_7 nerve root only. Intraneural blood flow in the nerve root was measured with a tissue blood flowmeter using the electrolytic hydrogen clearance method. Motor NCV was determined by stimulating the left L_7 nerve root using an electronic stimulator and recording muscle action potentials in the gastrocnemius muscle. There was a reduction of the intraneural blood flow in the nerve root after 1-day post–disc incision that was statistically significant when compared with a sham group of animals. The NCV began to be reduced 3 days after disc incision and was statistically significant on day 7, whereas the sham group demonstrated normal NCV throughout the testing period. The authors concluded that the reduction of the nerve root blood flow is one important pathophysiologic mechanism for NP-induced nerve injury.

Biochemical Mediators in Herniated Disc Tissue

Neuropathic pain can occur as a consequence of nerve trauma, with physical damage to nerves altering pain perception and the function of pain transmission

pathways. However, neuropathic pain can also occur in the absence of any detectable physical injury. In these situations, pathological pain appears to be a consequence of immune activation and inflammation, which can also amplify pain as a consequence of physical trauma. The role of immune activation in neuropathic conditions has been firmly established, and a consistent picture has emerged from these models of traumatic and/or inflammatory neuropathic pain. The key cellular mediators are most likely inflammatory cells recruited into the affected area from the general circulation along with locally stimulated cell populations. These cells produce proinflammatory cytokines (tumor necrosis factor [TNF], IL-1, IL-6) within the affected area and create and maintain pathological pain.

Takahashi and colleagues (1996) led one of the first investigations that used human specimens acquired during surgery. The tissue adjacent to the nerve roots at the herniation was excised and analyzed for the presence of proinflammatory cytokines. All tissue specimens contained detectable amounts of IL-1α, IL-1β, TNF-α, and IL-6. Although the findings are clearly intriguing, limitations include the absence of quantified levels of cytokines and a lack of normal discs for comparison. Furthermore, there was no attempt to measure pain perception using a reliable and valid pain instrument.

Kang and others (1997) cultured normal and herniated human intervertebral disc specimens to study the effects of IL-1β on the production of nitric oxide, IL-6, prostaglandin E_2 (PGE_2), and MMPs. Herniated cervical and lumbar intervertebral disc specimens were collected from patients undergoing surgery for radicular symptoms. Normal intervertebral disc specimens (cervical and lumbar) were obtained from patients undergoing surgery for traumatic burst fracture or lumbar scoliosis surgery. These specimens served as the control group. Tissue samples were then cultured in the presence or absence of IL-1β for 72 h. Normal, nondegenerated disc specimens increased production of MMPs, nitric oxide, IL-6, and PGE_2 in the presence of IL-1β. Herniated disc samples had higher levels of nitric oxide, IL-6, and PGE_2 than did normal disc samples, but the production increased significantly in the presence of IL-1β. Although this study did not correlate pain indices with production of these molecules, it did establish IL-1β as an inducer of degenerative and pain-producing molecules. It also demonstrated that the biochemical mechanisms of the intervertebral disc are vulnerable to the influences of biologic stimuli, and it illuminated a mechanism of disc degeneration. Induction of MMPs leads to excessive breakdown of the disc matrix, whereas nitric oxide, IL-6, and PGE_2 impair matrix synthesis.

Miyamoto and others (2000) analyzed herniated lumbar discs for the presence of IL-1β, TNF-α and cyclooxygenase (COX)-2, which induces the synthesis of PGE_2 during inflammation. The authors compared herniated specimens with normal discs obtained from patients undergoing anterior lumbar fusion for traumatic burst fracture. Their results demonstrated that COX-2, IL-1β, and TNF-α are present within the cytosol of the chondrocytes constituting the lumbar disc in all herniated specimens but not in any samples of normal disc tissue. When chondrocytes of the herniated disc were stimulated with IL-1β, a remarkable increase in the production of PGE_2 was observed. Although this study did not report any statistical analysis of the data, it did suggest a role for inflammatory cytokines in the production of PGE_2, an inflammatory mediator known to induce pain and to enhance pain sensitivity (Watkins and Maier 2000).

Roberts and colleagues (2002) compared expression of cytokines in herniated and nonherniated discs and found that all herniated samples had immunologically detectable IL-1β, whereas fewer had detectable IL-6, MCP-1, thromboxane, or TNF-α. Nonherniated discs had little or no detectable levels of these molecules. Interestingly, when detected, these molecules were strongly associated with blood vessels. Statistical analyses were not reported.

Burke, Watson, McCormack, Dowling, and others (2002) compared disc tissue from patients reporting sciatica with that of patients who were undergoing surgery for discogenic low-back pain. Specimens from patients undergoing lumbar discectomy were collected in which some had the annulus intact, some had nuclear extrusion, and some were sequestrated. Other specimens were collected from patients undergoing lumbar interbody fusion for discogenic back pain, of which some had the annulus intact and some were extrusion herniations. Significant quantities of IL-6, IL-8, and PGE_2 were produced by tissue samples in both the sciatica and low-back pain groups. None of the specimens produced TNF or IL-1. There was a signifi-

cant linear relationship between the production of IL-6 and IL-8. Specimens of sequestrated disc from the sciatica group produced inflammatory mediators in quantities similar to the low-back pain group. A major weakness of this study was the absence of pain indices and functional status among patients. This may have provided insight regarding the relationship between pain, function, and cytokine levels. Furthermore, although significant, correlations were low, suggesting that other factors may be involved.

Specchia and others (2002) investigated the cytokine profiles from herniated disc tissue among patients undergoing discectomy who reported symptoms of sciatica lasting longer than 1 year. Only protruded intervertebral discs bulging into the spinal canal without breach of the posterior longitudinal ligament were studied. Autopic L_{4-5} disc tissue from age-matched subjects with no history of back pain were used for control. Transforming growth factor-β1 (TGF-β1) was expressed in herniated discs, particularly in chondrocytes, endothelial cells, and in the granulation tissue of the surrounding matrix. Insulin-like growth factor-1 (IGF-1) was present in chondrocytes of both normal and pathological tissue, with a stronger labeling in the latter. IL-6 and IL-6R (IL-6R) immunoreactivity was detected in the cytoplasm of chondrocytes of the protruded intervertebral discs. Herniated disc tissue exhibited significantly increased levels for all cytokines compared with normal disc tissue. This study provided the first demonstration of the expression of IL-6R in the chondrocytes of herniated tissue and confirmed the presence of TGF-β1, IGF-1, and IL-6, factors released in response to tissue damage, in herniated disc tissue.

Alterations in the Biochemical Environment of the IVD

Together, these studies provide compelling evidence of NP-induced effects on adjacent nerve root(s), including nerve conduction velocity, mechanosensitization, pain behavior, histological degeneration, reduced blood flow, and increased endoneurial fluid pressure. The biochemical changes initiated by exposed NP and the increased production of proinflammatory cytokines create an environment of degradation. This process has been hypothesized to be part of disc resorption, influenced by migrating macrophages (Benoist 2002). In any case, the synergistic effects of nerve compression and the altered chemical environment of the IVD appear to produce the pathophysiologic network leading to the pain experienced by those with herniated discs.

To identify the specific proinflammatory mediators involved, Onda and others (2002) studied the effects of exogenous application of TNF-α on noci responses of dorsal horn neurons in the spinal cord at L_5 using anesthetized rats. Gelfoam containing 1 mm^3 of rat recombinant TNF-α or saline was applied to the nerve root trunk just cranial to the DRG for 2 h. The mean firing rate in spontaneous discharges of neurons was recorded every 15 min. In the TNF-α-treated group, the mean rate of spontaneous discharge of neurons began to increase at 1 h after TNF-α application and lasted until the end of recording (120 min). In the DRG of the TNF-α group, interstitial edema and enlarged capillaries were observed at 2 h postapplication. The control group showed no apparent morphological changes. The results suggest that a small production of TNF-α at the site of the nerve root may cause ectopic discharges in the primary afferent fibers and thereby induce prolonged excitation in the pain-processing neurons responsible for radicular pain contributing to hyperalgesia and spontaneous pain.

Aoki and others (2002) used pigs to study the effects of epidural application of NP, IL-1β, TNF-α, interferon-γ, or fat on NCV. Application of fat resulted in a normal NCV 7 days later (74 ± 10 m/s) whereas the NCV in the NP group was significantly reduced (40 ± 18 m/s). Both the IL-1β and INF-γ displayed reduced NCVs (64 ± 27 m/s and 60 ± 15 m/s), but the reductions were not statistically significant. However, in the animals treated with TNF-α, a significant reduction of the velocity was observed that was more pronounced than that of the NP (32 ± 12 m/s). Although this study did not include pain indices, it does strengthen the possible role of TNF-α as the main mediator responsible for reducing NCV in the nerve root.

Ahn and colleagues (2002) investigated the correlation between the presence of cytokines and radicular symptoms in patients undergoing microdiscectomy. Radicular symptoms were assessed by motor, sensation, reflex, degree of pain onset in the straight-leg-raising test, and development of radicular pain by back extension in 3 prone positions: full extension, elbow support, and lying prone. All patients were asked to re-

port their pain using a visual analog scale (VAS). The messenger ribonucleic acids (mRNAs) of IL-8, TNF-α, IL-1α, RANTES, and IL-10 were expressed in 70%, 65%, 39%, 17%, and 9% of the herniated disc specimens, respectively. Furthermore, a significant association between IL-8 mRNA expression and the development of radicular pain by back extension and radicular pain by elbow support on prone and lying positions was observed. The mRNA expression of cytokines was not associated with the degree of pain onset in the straight-leg-raising test and pain scoring according to the VAS. From this study, IL-8 appears to be a pivotal chemokine involved in the evolution of radicular pain.

Summary of Research Studies

Replicating human disorders of the IVD in animals has proven difficult, as humans are the only obligate bipedal vertebrate. However, animal models have provided clues into the pathophysiologic effects of proinflammatory cytokines and have assisted in generating new ideas for potential therapeutic treatment. In addition, attaining satisfactory control in studies of random samples of human tissue has been equally challenging. For instance, disc tissue procured during surgery is usually cut into portions, thereby making it almost impossible to determine the exact structure of the herniation actually involved in situ (protrusion vs. extrusion vs. sequestration) or the type of tissue procured (nucleus pulposus vs. annulus fibrosis). Included in this conundrum are the elements of lifestyle, body weight, and aging, all of which influence the load environment of the normal IVD. Lifestyle and body weight are capable of accelerating the rate of degeneration and thus further complicating the starting point from which to assess IVD degeneration.

The studies to date provide evidence of connective tissue degradation, nerve and vessel ingrowth, and increased production of proinflammatory cytokines that characterize IVD degeneration and herniation. There is considerable need for more investigation into the precise role of cytokines for each of these biological processes. Concurrently, the study of immune involvement in neuropathic pain is in its infancy. Many more immune cells and immune-derived substances may be implicated in the etiology of pathological pain syndromes. Much remains to be learned about the dynamics of immune system modulation of pain and neural function.

Interestingly, to date, psychological measures and the effect of stress on cytokine production have been completely ignored. Yet one's psychological perception has the potential to modulate biological mechanisms implicated in back pain and sciatica. A large body of evidence demonstrates that perception of stress and the resultant mood disturbance (depression and anxiety) lead to enhanced proinflammatory cytokine production. This has been demonstrated in numerous human paradigms and provides the linkage between the nervous and immune systems and cytokines (Biondi and Picardi 1999; Witek-Janusek and Mathews 2000). Hence, the need to investigate possible correlations between biological mechanisms of pain (i.e., cytokines) and psychological factors that modulate the production of cytokines and the patient's experience of pain are evident and need to be addressed in future studies.

Conclusions and Clinical Implications

The recognition that the immune system may be involved in neuropathic pain has important potential implications. If proinflammatory cytokines contribute to pain and to neuropathological changes in the sensory neurons, it may be possible to devise much-needed alternative approaches for treatment of patients with low-back pain. Surgery for herniated discs is not without cost, and surgical treatment of disc herniation is advised only if nonsurgical treatment fails. Furthermore, resolution of pain is not guaranteed with surgery, as complications and failure rates remain relatively high (Cooper and Freemont 2004). Understanding the role of the immune system in disc-related pain may lead to a better appreciation of not only the nature of organic pain but also alternative therapeutic approaches or drug strategies to treat pain and its antecedents. Moreover, the evaluation of immune markers as indices of pain and of immune responsiveness consequent to pain may provide insight into the means by which to fine-tune the therapy provided to individual patients.

One such study involving diagnostic criteria suggests that Modic changes may be an objective marker

of discogenic low-back pain. Modic changes are signal intensity changes on plain radiograph x-rays and magnetic resonance imaging that reflect a spectrum of vertebral body marrow changes associated with degenerative disc disease. A correlation between Modic changes on spinal magnetic resonance images and the production of proinflammatory cytokines was analyzed by Burke, Watson, McCormack, Fitzpatrick, and others (2002). They demonstrated a statistically significant increase in the levels of IL-6, IL-8, and PGE_2 in the disc tissue of patients with Modic changes. Modic 1 changes were more common in patients with discogenic low-back pain, whereas Modic 2 changes occurred in patients suffering from sciatica.

Traditional treatment for low-back pain includes nonsteroidal anti-inflammatory medication, which inhibits prostaglandin synthesis, as first-line therapy. Patients exhibiting sciatic symptoms are often prescribed steroids (by mouth or epidurally) to decrease swelling in the affected nerve root. The use of these substances in long-term therapy, however, must be weighed against their side effects. Gabapentin has been added to the armamentarium for treating neuropathic pain. Although its mechanism of action is unknown, it is structurally related to the neurotransmitter γ-aminobutyric acid. All of these medications have limited success in relieving symptoms of low-back pain and sciatica, and none prevent progression of degenerative disease.

The recognition of peripheral and central immune cell involvement in neuropathic pain of diverse etiologies may offer a new avenue or approach to pain control. There are multiple situations in which immune-derived proteins (TNF, IL-1, IL-6) have been correlated with and are the likely cause of neuropathic pain conditions (Watkins and Maier 2000). The pervasive and potentially key involvement of these proinflammatory cytokines within an affected body region or within the spinal cord are likely and desirable targets for drug development.

In a novel attempt to evaluate selective inhibition of TNF-α in NP-induced nerve injury, Olmarker and Rydevik (2001) used autologous NP applied to the porcine sacrococcygeal cauda equina. The pigs were subsequently given systemic treatment with selective TNF-α inhibitors, etanercept, or infliximab. Soluble TNF-α receptors (etanercept) and selective antibodies (infliximab) were used at therapeutic concentrations. The comparison group was treated with a heparin analog (enoxaparin) to evaluate whether the prevention of NP-induced nerve conduction velocity reduction was linked to a corresponding reduction of intraneural thrombus formation and edema. The control group had saline applied. After 7 days, the NCV over the application zone was determined. The NCV was similar between the saline and the enoxaparin groups at approximately 50 m/s. In contrast, both the etanercept and the infliximab groups displayed mean values of nerve conduction velocities close to normal. Nerve fiber injury was statistically less pronounced in the etanercept and the infliximab groups compared with the enoxaparin and saline groups, implying that nerve inflammation induced by the NP was mediated by TNF-α. The group treated with enoxaparin exhibited no differences in NCV or histology compared to the control group.

In a similarly designed study, Olmarker and others (2003) evaluated the use of selective TNF-α inhibition on spontaneous behavior in the rat model of experimental disc herniation. After exposure, the L_{4-5} intervertebral disc was incised and injected with a small amount of air. Sham exposure, in which the L_{4-5} vertebrae were visualized, served as a control. Some of the rats received an intraperitoneal injection of 0.125 mL of 10 mg/mL infliximab, a known TNF-α inhibitor that exerts its effects through specific inactivating antibodies, before surgery. Behavioral analyses were performed the day before surgery and on days 1, 3, 7, 14, and 21 after surgery. No difference in immobilization behavior was observed in the rats for the first 14 days. At day 21, there was a statistically significant higher immobilization in the rats in the nontreated NP series as compared to the sham. Locomotion was reduced in both groups exposed to NP at each time point, although the nontreated group showed a statistically significant reduction as compared to the sham group. Lifting of the leg on the operated side in the nontreated NP group was increased significantly compared to the sham and treatment groups at days 1 and 3. Rotating the head toward the leg on the operated side was statistically significant in the nontreated NP group at days 3 and 7 only, whereas this behavior was not observed in

the other 2 groups. This study reflects the altered behavioral patterns induced by exposed NP in rats. Moreover, it adds evidence that TNF-α is a prime inducer of these effects.

To date, only 1 small pilot study among humans ($N = 10$) has been performed to evaluate the effectiveness of TNF-α blockade among herniated disc patients (Karppinen and others 2003). The results demonstrated that a single infusion of infliximab was highly effective in reducing sciatic pain by a mean of 49% within 1 hour of the infusion. This benefit was maintained even 6 months postinfusion, with the result that none of the subjects underwent surgery and all returned to work within 1 month of the infusion.

Freemont, Watkins, Le Maitre, Jeziorska, and others (2002) are currently examining the role of gene therapy in disc degeneration. Using genes introduced into target cells, proteins are produced within the degenerate disc, which provide a chemical environment conducive to restoring cell function toward normality.

Although some pathologic conditions require immediate decompressive surgery, as in cauda equina syndrome, the role of surgery in disc degeneration syndromes is becoming less clear. As new therapies continue to evolve that are able to target the biochemical factors involved in pain transmission, perhaps the ultimate test will be whether a pathway can be found that reverses the degenerative condition.

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