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Pathophysiology of inflammatory, degenerative, and compressive radiculopathies

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A 42-year-old woman presents with the chief complaint of left lower extremity pain that began approximately one month ago after she lifted a bag of groceries. Her discomfort affects the lower lumbar region and buttock, extends to the lateral thigh and calf, and terminates over the proximal foot dorsum. These complaints are particularly pronounced while sitting or performing bending and lifting maneuvers. Her physical examination findings are significant for a provocative straight-leg raise, 4+ hip abductor and ankle dorsiflexor weakness, and a diminished left medial hamstring reflex. An MRI of the lumbar spine demonstrates extruded disc material posterolaterally to the left at L4-5 that is observed to displace the L5 nerve root on its exit from the thecal sac. Her condition has failed to improve despite recent activity modification and the regular use of oral anti-inflammatory agents and analgesics.

A treatment plan is presented that includes fluoroscopically guided therapeutic transforaminal injections on the left at L5 and the introduction of mechanical exercises and a lumbar spine stabilization program. At this point, the patient asks, “How is all of this going to help my herniated disc?” If physicians are to accurately educate their patients with radicular syndromes, the answer to this question should be descriptive of the multiple pathophysiologic processes that are believed to contribute to neural irritation and injury. The purely mechanical concept of radiculopathy is likely too simplistic. This patient’s focused and appropriate question affords an opportunity to introduce the mechanochemical injury construct.

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Mechanical

The relationship between lumbar intervertebral disc rupture and “sciatica” initially was described by Mixter and Barr in 1934 [1]. Semes and Murphey [2] described similar acute cervical disc pathology resulting in “radiculitis” in 1943. Verbiest [3] drew attention to the role of developmental narrowing of the lumbar canal in radicular syndromes in 1954, and compression of the lumbosacral nerve roots arising in the setting of degenerative stenosis was described as early as 1931 [4]. Stenotic upper extremity pain syndromes occurring in the setting of degenerative “cervical arthritis” with resultant irritation of the cervical nerve roots was recognized by 1943 [2].

Each of these landmark articles contributed to the understanding of the mechanical component of radicular pathology. Spinal nerve roots and their nutrient vessels lack a perineurium and demonstrate a poorly developed epineurium, rendering them particularly vulnerable to mechanical injury. Additionally, the blood supply to spinal nerve roots is not as secure as that to their peripheral nerve counterparts [5–7]. It is likely that the most pertinent mechanical effect of herniated disc material or degenerative stenosis on neural tissue is one of increased pressure [5]. In vivo studies of the effect of pressure on nerve roots have revealed that the first effect probably is one of impaired venous blood flow within the vasa nervorum, which can be observed initially with compressive pressures as low as 5 to 10 mm Hg. At these levels, capillary stasis and ischemia have been observed [8]. Partial blockage of axonal transport also can be observed with pressure as low as 10 mm Hg [9]. At approximately 50 mm Hg, local capillary permeability increases, resulting in an extravasation of albumin and local edema [10]. Nerve conduction failure first occurs when pressures of 50 to 75 mm Hg are sustained for 1 to 2 hours, and neural ischemia can be complete with compressive exposures that reach 70 to 130 mm Hg [7].

Although local compression of neural tissue may induce direct structural insults, including deformation of the nodes of Ranvier and paranodal myelin, such effects typically occur with higher sustained pressures. The injuries more commonly observed in association with lower compressive exposures (ie, less than 200 mm Hg) likely arise in the setting of impaired blood and nutritional supply to neural tissue [7].

As opposed to a more graded compressive injury, edema formation in nerve roots has been shown to be particularly pronounced with rapid compression [10]. This finding may suggest that neural tissue is better able to accommodate to a gradually evolving structural compromise, such as degenerative stenosis, as opposed to a more acute discogenic or traumatic compressive insult.

Spinal nerve mechanical injury may be particularly pronounced within the neural foramen, where sensory and motor roots and the dorsal root ganglion (DRG) are encased by a rigid nerve root sleeve [10]. Compression of the periradicular venous plexus within the foramen and resultant blood stasis can lead

to congestion, ischemia, intraneural edema, and increased intraneural pressure [11]. The DRG is of particular interest because it seems to be quite vulnerable to mechanical stimulation. The DRG has been shown to fire repetitively after minimal compression and likely demonstrates even greater mechanosensitivity in the setting of chronic injury [12,13]. In addition to these more direct compressive effects, mechanical stressors also can result in a loss of normal nerve mobility. Nerve roots and spinal nerves typically demonstrate 2 to 5 mm of glide within their neural foramen [14]. In a compressive injury, injured nerve roots may become tethered to their surrounding structures, possibly resulting in a loss of normal glide and rendering the nerve vulnerable to further tensile and stretch-type irritation during movement [15].

Although these multiple adverse mechanical effects on neural tissue are well described, recent clinical and radiologic studies suggest that the mechanism of injury in radiculopathy is a more multifactorial process. Experimental operative studies have shown that although minor manipulation of an inflamed nerve root typically is painful, compression of normal nerve roots usually does not elicit a painful response [6,16–18]. This finding was described initially in 1958 by Smythe and Wright [18], who placed nylon threads on normal nerve roots intraoperatively. With tension applied postoperatively, no resultant pain was described. During decompressive surgeries performed with the use of progressive local anesthesia, Kuslich et al [16] similarly observed that the normal or uncompressed nerve root could be manipulated with associated paresthesias but without significant pain. Radicular pain could be produced only through stimulation of a swollen or stretched nerve root. Once again, the same observation may not hold true for the particularly sensitive DRG. Acute compression of a normal DRG can result in sustained repetitive firing [12,13].

An investigation of lumbar MRIs of asymptomatic patients revealed herniated discs in 20% of those younger than 60 years and stenosis in 21% of older individuals [19]. A similar study of the cervical MRIs of asymptomatic patients revealed herniated discs in 10% of those younger than 40 years and neural foraminal stenosis in 40% of those older than 40 [20]. These findings in patients without radicular symptoms suggest that the presence of an acute discogenic or degenerative stenotic stressor often does not result in radicular symptoms. Additional studies have investigated the natural history of symptomatic cervical and lumbar disc lesions. When patients are followed with serial imaging, larger and extruded offending discs are found to resorb the most, and many acute disc herniations are observed to reduce in size by 50% to 100% [21–23]. Of particular interest is the observation that patients with extremity complaints typically improve before the morphologic resolution of their disc lesion [24]. This finding offers further support for additional and nonmechanical contributing factors in the pathophysiology of radiculopathy. A more recent clinical investigation demonstrated no correlation between nerve root contact pressure from an acute disc herniation and the limitation in straight leg-raise testing [25]. These observations

compel the spine clinician to consider the nonmechanical and less visible stressors that likely contribute to radicular pathology.

Biochemical

Although the mechanical stressors contributing to radicular syndromes were well described by the 1940s, it was not until the early 1970s that the chemical and inflammatory components of neural injury were first identified. In 1973, Marshall and Trethewie [26] stated: “We consider the acute pain in disc is due to local irritation of the nerve-root producing oedema and release of protein and H-substances at the site of disc injury. Relief of pain by cortisone accords with these findings....” This article set the stage for further investigation of the chemical component of neural injury.

The epidural application of nucleus pulposus to cauda equina nerve roots in pigs, without associated mechanical nerve root compression, was observed to result in a pronounced reduction in nerve conduction when compared with the similar application of a fat control. The application of nuclear material also resulted in a more pronounced histologic injury than that observed in controls. Such findings suggest that there may be a direct biochemical effect of nucleus pulposus material on neural tissue that results in inflammatory, microvascular, and structural injury [27]. In a dog model, the effects on nerve roots after the incision of an adjacent annulus fibrosus were similarly investigated. Once again, without a more apparent mechanical stressor, resultant capillary stasis, significantly reduced conduction velocity, and structural axonal change were observed. These findings suggest that an annular tear, which might not be radiologically visible, and the subsequent leakage of nucleus pulposus can contribute to the pathophysiology of radiculopathy [28]. Similarly, synovial cytokines have been shown to impair sciatic nerve function in a rat model, raising the possibility that leakage of synovial fluid from an adjacent zygapophyseal joint might contribute to radicular pathology [29].

In a controlled behavioral study using a rat model, chronic gut sutures were applied loosely to the lower lumbar nerve roots. In these animals, the recovery from thermal hyperalgesia seemed to depend, in part, on the reduction of local phospholipase A2 activity after ligature introduction. In those groups in which corticosteroid was introduced epidurally, a more pronounced reduction of phospholipase A2 activity and a more rapid return to normal behavior were observed [30]. A review of the literature finds several studies that have identified multiple known inflammatory mediators at the site of disc herniation and nerve injury. High levels of phospholipase A2 have been identified in herniated disc material in patients undergoing discectomy for radiculopathy [31,32]. Increased levels of cytokines, leukotrienes, nitric oxide, immunoglobulins, and interleukins also have been detected at the site of disc injury [33]. A recent award-winning study specifically

investigated the potential role of tumor necrosis factor (TNF)- α in sciatica associated with herniated lumbar discs. Exogenous TNF- α was applied in an *in vivo* rat model and resulted in neuropathologic and behavioral changes markedly similar to those observed with the application of nucleus pulposus. These findings suggest that TNF- α may be a key player in the pathophysiologic processes leading to radicular pain [34].

Immunohistologic studies of herniated lumbar disc tissue have identified increased levels of cyclo-oxygenase 2 (Cox-2) and prostaglandin E₂ (PGE-2) [35,36]. Through the selective blocking of Cox-2, PGE-2 synthesis also was noted to be distinctly suppressed, suggesting that Cox-2 and associated inflammatory cytokines might contribute to radiculopathy through an upregulation of prostaglandin synthesis [36]. It was similarly observed that the introduction of a Cox-2 inhibitor in a rat model of radiculopathy resulted in a reduction in mechanical allodynia. Pain behavior was significantly lower in both the systemically and the intrathecally treated groups when compared with a control. The intrathecal treatment group demonstrated the greatest and a statistically significant attenuation of allodynia. Studies of the role of inflammation in radicular syndromes have also shed light on a potentially associated systemic inflammatory process and elevated plasma C-reactive protein levels in response to local nerve root injury [37].

Although multiple inflammatory mediators have been identified at the site of disc injury, the relationship between clinical symptoms and the presence of inflammatory cells such as macrophages, leukocytes, and neutrophils remains less clear [38]. An immunohistochemical analysis of 96 transligamentous disc herniations was performed and correlated with patients' motor weakness and response to straight leg-raise maneuvers. A significant relationship between the presence of inflammatory cells and clinical symptoms was not identified. Only activated T cells demonstrated a limited correlation with straight leg-raise limitation. The authors concluded that macrophages were probably more active in disc resorption than in the pathologic processes contributing to sciatica [39]. A study of 179 disc samples from patients who had undergone discectomy also attempted to correlate preoperative clinical data and visual analogue scores with macrophage tissue infiltration. After statistical analysis, although varying amounts of inflammatory cells were identified, no significant correlation between macrophage presence and the recorded clinical data could be identified [40]. Because mast cells are known to play an important role in inflammatory processes, their presence in herniated lumbar disc samples has also been studied. Fifty herniated lumbar disc samples were obtained from patients who had undergone discectomy and compared with control disc samples. Only a minority of disc herniations demonstrated mast cells after toluidine blue staining and immunocytochemical analysis, with no sample demonstrating a pronounced mast cell infiltration. This finding suggests a similar limited role for mast cells in the inflammatory processes of radiculopathy after disc herniation [41].

Most of our understanding of the inflammatory and biochemical components of radiculopathy has arisen from both animal and human studies of lumbar disc pathology and neural injury. A study of cervical disc specimens removed after discectomy for radiculopathy also has been performed. These samples were compared with a control group of disc material removed during anterior surgery after traumatic burst fractures. When compared with the control group, significantly increased matrix metalloproteinase, nitric oxide, PGE-2, and interleukin-6 were identified. These observations were similar to those made in previous studies of lumbar disc material, suggesting that similar pathophysiologic processes likely were contributing in patients with cervical radiculopathy [42].

Pain generation and centralization

Patients with radicular pathology typically present with the chief complaint of pain. Pain and paresthesias often are referred to as positive symptoms of radiculopathy, whereas weakness and numbness are considered negative symptoms. Positive symptoms are believed to reflect neuronal hyperactivity, and negative symptoms may stem from diminished neural firing occurring in the setting of axonal loss or conduction block [5,43]. Using the technique of microneurography, in which microelectrodes are placed within the fascicles of peripheral nerves, it has been suggested that the more distal paresthesias of lumbar radiculopathy arise when activity in large sensory afferent fibers is generated ectopically. Such ectopic activity is presumed to occur from irritation of the nerve root or DRG [44].

As described previously, the DRG is a unique component of the spinal nerve, containing the cell bodies for the sensory neurons. The DRG is particularly sensitive to mechanical irritation and is suspected to be a key player in radicular pain syndromes. Because the DRG typically is located within the neural foramen [45], foraminal disc pathology or stenosis might be more likely to result in a burning or dysesthetic type of pain involving the affected limb [5]. In addition to the positive and negative symptoms originating from direct involvement of the spinal nerve and DRG, symptoms also may arise from activation of those surrounding pain generators that most likely are intimately involved in radiculopathy.

The spinal nerve dura mater is richly innervated by an extensive intraspinal neural plexus derived from the sinuvertebral nerves. This innervation is particularly pronounced over the ventral aspect of the thecal sac and around the nerve root sleeves [46]. The dura mater is both mechanically and chemically sensitive, and its stimulation can result in lumbar and lower extremity pain [47,48]. In radicular pain syndromes, in addition to those symptoms arising from direct nerve root involvement, irritation of the surrounding dura may result in local somatic and more distally referred symptoms to the extremity [46]. It has been suggested that the dysesthetic pain in nerve root injury stems from volleys of impulses beginning in damaged afferent fibers of

the spinal nerve roots, whereas the associated deeper aching discomfort might be caused by the activation of the *nervi nervorum* that innervate the neural and meningeal tissues [49,50].

The sinuvertebral nerve also innervates the posterior annulus of the intervertebral disc and posterior longitudinal ligament as well as the epidural veins. The zygapophyseal joints receive their innervation from the medial branches of the dorsal rami [46]. In the setting of acute disc pathology or degenerative stenosis leading to nerve root or spinal nerve irritation, these surrounding structures may contribute to axial and limb complaints. Studies using lumbar discography and provocative intra-articular zygapophyseal joint injections have demonstrated resultant symptom referral to both the proximal and the distal lower limb [51,52]. Through cervical discography, proximal and distal pain referral patterns affecting the upper limb have been described [53]. The innervated epidural veins, if distended because of stenosis or focal disc pathology, also may serve as a pain generator in radicular syndromes [46]. Each of these surrounding spinal structures has the potential to contribute to the pain experienced in radiculopathy by sending afferent impulses to the segmental DRG.

It has been demonstrated that nociceptors become sensitized and more responsive to subsequent noxious stimuli as time elapses after injury onset [54]. There is also evidence that central nervous system sensitization occurs after the shower of afferent impulses from peripheral nociceptors during the injury process [55]. In a controlled study of herniated disc material harvested during lumbar spine surgery, free glutamate was identified in concentrations sufficient to diffuse to glutamate receptors and activate the neurons of the DRG. In this study, radiolabeling of the DRG was observed when glutamate was introduced epidurally at concentrations significantly lower than that observed in herniated disc material [56]. In a controlled rat model of ligature-induced lumbar radiculopathy, spinal cord segments were harvested and sectioned for glial and cytokine immunohistochemistry. Glial activation and enhanced interleukin-1 β expression were observed in the spinal cord after injury, supporting a contributing central and neuroimmune component in the symptoms of radiculopathy [57]. A controlled study of somatosensory-evoked potentials in patients with cervical radiculopathy demonstrated increased spinal and cortical response amplitudes after digital nerve stimulation at the affected digit. The amplitude increases correlated positively with the extent of pain experienced by the patients. These findings also suggest that radiculopathy is associated with changes in neural activity at both the peripheral and the more central levels of the somatosensory system [58].

Fibrosis and chronic injury

Chronic nerve root irritation and edema may lead to fibroblast infiltration and fibrosis formation within the injured neural tissue [7]. Cadaver

studies have led to correlations among degenerative disc changes, dilation of epidural veins, intraneural and perineural fibrosis, and neural atrophy [11,59]. Prolonged impairment of a nerve root's nutritional supply also may lead to the accumulation of waste products. These products may include acidic components that can alter the local ionic balance within the nerve roots, leading to more sustained pain production [7]. The pathologic changes affecting the nerve roots of the cauda equina in more long-standing spinal stenosis have been described. Thickening of the meningeal membranes and fibrotic structural alterations were observed. Such findings similarly can lead to neural dysfunction by hindering the diffusion of nutrients from the surrounding cerebrospinal fluid [60,61]. Chronic fibrosis also can impair neural gliding, leading to superimposed stretch injuries that further contribute to the chronic injury process.

Summary

In answering the patient's question regarding how treatments are likely to "help [her] herniated disc," the mechanical and chemical components of radiculopathy should be addressed. Focal disc abnormalities often can be observed in those without pain, and symptomatic discs can become asymptomatic. Disc lesions can resolve radiologically with time, and patients' symptoms can improve before their radiographs. The literature reviewed in this article suggests that the best opportunity to offer therapies that address the chemical component of injury might be in those patients with acute disc pathology.

In the case of degenerative stenosis, gradually evolving mechanical stressors may comprise the primary component of injury. In other instances, patients with radiographic evidence of neural foraminal or lumbar central stenosis may become symptomatic secondary to a superimposed mechanochemical injury. Such stressors can include a focal disc protrusion, leaking nuclear material from an annular tear, or synovial fluid from an adjacent arthrotic zygapophyseal joint. In these patients, the successful treatment of the acute injury process might allow the affected neural elements to return to their state of accommodation in an environment of gradually evolving mechanical compromise.

A growing body of literature has helped clinicians to better understand the mechanisms behind radicular disorders. As spine clinicians, we should strive to educate our patients so that they may become more knowledgeable consumers of spine care. As the components of radicular pathology are elucidated further, new biochemical therapies will likely evolve. Similarly, there will probably always be a subset of patients who will require mechanical decompression, and some of these individuals should be offered such treatment without delay.

There may a time in the radicular injury process at which a window of opportunity for treatment begins to close. After this point, any therapy

offered will not be as likely to result in a more complete symptomatic response. Patients with chronic radicular pain may have neural structural insults and an increased sensitivity of the somatosensory system. Clinicians should strive to avoid this end stage of neural injury, which is less reversible from a chemical or mechanical standpoint and may respond only to chronic pain management modalities.

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