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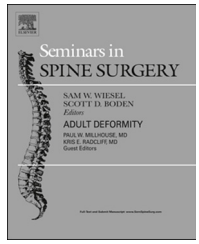

The epidemiology and pathophysiology of lumbar disc herniations

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ABSTRACT

Lumbar intervertebral disc herniations are the most common causes for working-age individuals to undergo lumbar spine surgery. Patients with a family history of disc disease or are in physically demanding jobs, or who have certain medical comorbidities such as obesity, are at an increased risk of developing a lumbar disc herniation. Symptomatic herniations present as lumbar radiculopathy from both a mechanical compression and chemical irritation of the nerve root.

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1. Introduction

Lumbar intervertebral discs (IVDs) are complex structures that undergo significant axial loading as well as flexion/extension, lateral bending and rotational forces. Because of the biomechanical demands placed upon these structures, as well as their inability to remodel due to their avascular nature, lumbar disc herniations are common. Lumbar disc herniations can lead to substantial radicular symptoms, which if persistent, may require surgical intervention.[1] The purpose of this article is to discuss the anatomy of the intervertebral disc, as well as the epidemiology and pathophysiology of lumbar disc herniations.

2. Anatomy of the intervertebral disc

Intervertebral discs are composed of the cartilaginous endplates, the annulus fibrosus (AF), and the nucleus pulposus (NP).[2] The endplates are a transitional structure between the subchondral bone of the vertebral bodies and the AF of the intervertebral discs, and different authors have grouped the endplate as part of the vertebral body, the intervertebral disc or as a separate structure.[2,3] The endplates are made of a 1-mm thick layer of hyaline cartilage, which is comprised of 50% water, chondrocytes, proteoglycans (PGs), and type II collagen.[4] Additionally, this cartilaginous layer has a substantial capillary network that may extend one to two millimeters into the AF. This vascular network is responsible for providing all the nutrients to the otherwise avascular intervertebral disc.[5]

The AF is the outer ring of the intervertebral disc, and is comprised primarily of fibroblast-like cells and obliquely oriented type I collagen fibers.[3] While it is comprised of 15–25 lamellar rings, it is commonly divided into the outer and inner AF.[2] The outer layer is highly organized and almost exclusively made of type I collagen, resulting in high tensile strength. Comparatively the inner layer is a transitional zone between the AF and NP and has both type I and type II collagen, as well as multiple different proteoglycans.[6]

The NP is center portion of the intervertebral disc, which is responsible for the ability of the intervertebral disc to withstand substantial axial loads. Chondrocyte-like cells secrete type II collagen, as well as numerous PGs. Aggrecan is the most common PG in the NP, and its large negative charge is responsible for the substantial hydrophilic nature of the NP.[3] Lastly, notochordal cells have recently been identified in the NP, and these cells are responsible for stimulating the

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collagen and PG production, as well as preventing apoptosis of the chondrocyte-like cells.[7,8]

3. Defining a lumbar disc herniation

Prior to discussing the epidemiology and pathophysiology of a herniated lumbar disc, it is critical to have a clear definition a lumbar disc herniation (Fig. 1). While often times the terms disc herniation, disc protrusion, and disc bulge are used interchangeably in the literature, according to the combined task forces of the North American Spine Society, the American Society of Spine Radiology, and the American Society of Neuroradiology, these pathologies are not the same; they define a disc herniation as "localized or focal displacement of disc material beyond the limits of the intervertebral disc space."[9] This distinction is critical, because it establishes that diffuse annular expansion extending beyond the disc space (a disc bulge) is not a disc herniation, but rather a form of disc degeneration. A true herniated disc is a focal pathology that affects less than 25% of the intervertebral disc.[9] Herniated discs can be categorized as protrusions, extrusions, or sequestrations (Fig. 2). Protrusions are wide-based herniations in which the diameter at the base of the herniation is wider than the diameter of the herniation in the canal. Extrusions have a narrow base, with a large herniation in the canal, and sequestrations are herniations in which there is no continuity between the herniation and the remaining intervertebral disc.[9]

4. Epidemiology of lumbar disc herniations

Significant research into the epidemiology of lumbar disc herniations has been performed, and many possible risk factors have been identified. In an analysis of patients enrolled in the intervertebral disc arm of the Spine Patient Outcomes Research Trial (SPORT), Cummins et al.[10] reported that the average age of patients with a herniated disc was 41 years, and the diagnosis was slightly more common in males than females (57% versus 43%, respectively).

An elevated body mass index (BMI) is a risk factor for lumbar disc herniation, and it is thought to be due to the increased axial load on lumbar spine.[11] In a Finnish study, Bostman reported 27% of the patients undergoing surgery for a lumbar disc herniation were obese, whereas the population prevalence of obesity in Finland at that time was only 16%. Similarly, a recent meta-analysis found that overweight patients (BMI: 25–30) and obese patients (BMI $>$ 30) had a statistically significant increase risk of being diagnosed with lumbar radiculopathy than patients with a BMI $<$ 25.[12] Furthermore, obesity has been linked to an increased risk of recurrent disc herniations after a microdiscectomy, as Meredith et al.[13] reported obese patients (BMI $>$ 30) were 12 times more likely to have a recurrent herniation, and 30 times more likely to undergo a revision surgery than non-obese patients.

Other medical comorbidities such as diabetes, hyperlipidemia, and smoking have also been reported as possible risk factors for lumbar disc herniations. Sakellaridis compared a case series of 102 patients requiring surgical intervention for a lumbar disc herniation to 98 patients undergoing elective surgery for another reason and found a statically significant increase in the rate of diabetes in patients undergoing a lumbar microdiscectomy (32% versus 19%, $p = 0.001$). Furthermore, Mobbs et al.[14] reported that the needed for revision surgery for diabetic patients was 7 times higher than non-diabetic patients. Similarly, in a case–control study, Longo et al.[15] reported that plasma concentration of triglycerides and total cholesterol was elevated in patients with a lumbar disc herniation. Lastly, a recent meta-analysis of 49 articles identified smoking as an independent risk factor for lumbar disc herniations.[16] While the mechanism by which these comorbidities increase the rate of lumbar disc herniations

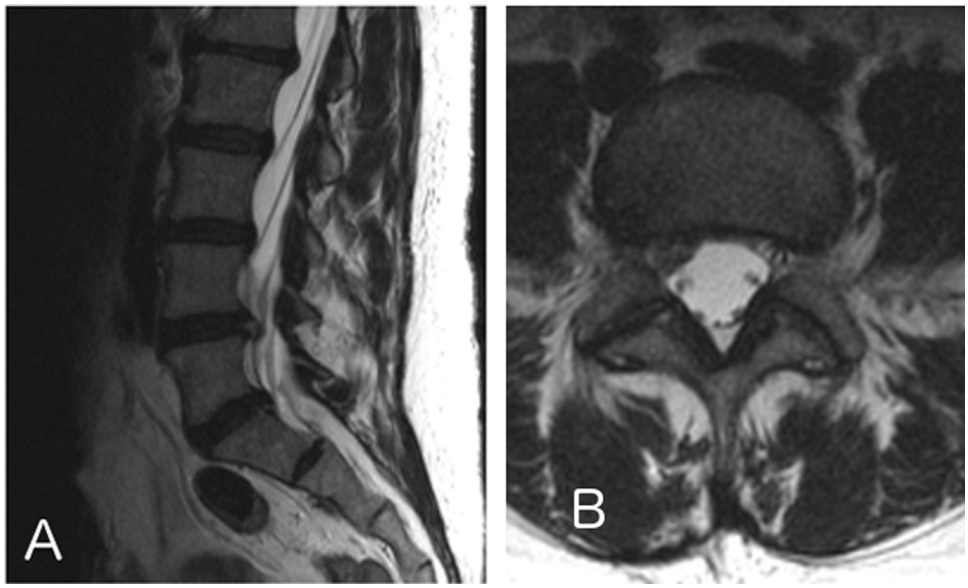

Fig. 1 – A 40-year-old female with persistent L5 radiculopathy. Sagittal (A) and axial (B) T2 MRI images, demonstrating a right poterolateral L4/5 herniated disc

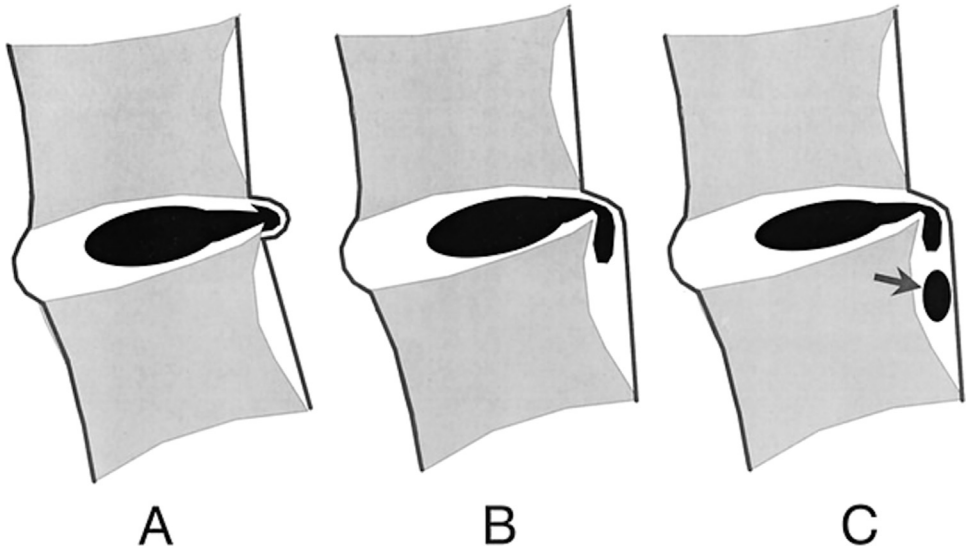

Fig. 2 – Schematic drawing representing a protrusion (A), an extrusion (B), and a sequestration (C).

has yet to be definitively proven, authors have speculated that these comorbidities may either lead to a decrease in the microcirculation to the intervertebral discs or an alteration in the cytokine expression. Either of these mechanisms could then lead to annular degeneration and an increased risk of a lumbar disc herniation.[11,15]

Occupational risk factors for lumbar disc herniations have been extensively studied, as this pathology is more common in working aged individuals than other lumbar spine disorders. Cummins et al.[10] reported that 20% of the patients in lumbar disc herniation arm of the SPORT had a workers' compensation claim, compared to only 8% of patients with spinal stenosis and 7% of the patients with a degenerative spondylolisthesis. Furthermore, multiple biomechanical studies have demonstrated that the combination of an axial load and twisting mechanism or an axial load and a flexion mechanism can lead to a herniated disc.[17,18] In the Copenhagen Male Study, a prospective epidemiologic cohort study of over 5000 men, strenuous physical activity at work was the most significant risk factor [hazard ratio of 3.90 (1.82–8.38)] for a subject requiring hospitalization for a lumbar herniated disc.[19] Furthermore, in a multi-center, case–control study, Seidler et al.[20] found a dose–response relationship between the total work-related lumbar load and the incidence of lumbar disc herniations.

While the increase in lumbar disc herniations with heavy lifting seems intuitive, studies have shown that it is not just manual labor that may increase the risk of a lumbar disc herniation. In a separate study by Seidler et al.,[21] lumbar disc herniations were significantly higher in patients who were in high stress jobs, specifically patients whose jobs resulted in repeated time-based deadlines, and patients with lower job satisfaction. Similarly, in a case–control study of over 4000 Chinese patients, Zhang et al.[28] found a statistically significant increase in the rate of lumbar disc herniations in patients who reported having substantial time pressure in their job.

Additionally patients who spend significant time driving may also be at an increased risk for lumbar disc herniations.[16,22] Two different mechanisms have been proposed for how driving may lead an increased risk of disc herniation. The first is that sitting decreases the lumbar lordosis, which increases the load through the posterior portion of the intervertebral disc. This alteration in load distribution then increases the risk of a posterolateral disc herniation.[23] The second is that the constant vibration from the vehicle may lead to a weakening of the posterior annulus. However, while multiple case series have reported lumbar disc herniations in professional drivers,[24–26] a recent case–control study of over 1000 patients, as well as a meta-analysis found no statistical increased risk of lumbar disc herniations in patients whose occupation involves significant driving.[16,22]

Finally, there is a clear genetic link to lumbar disc degeneration and lumbar disc herniations.[27] In a case–control study of over 4000 patients, Zhang et al.[28] reported that a family history of a lumbar disc herniation was the most important risk factor in predicting patients who would develop a lumbar disc herniation (odds ratio = 3.6). While the genetics behind lumbar disc herniations are likely multifactorial, a possible pathway has been described. The collagen IX tryptophan allele (Trp2) has been linked to an increased severity of disc degeneration in patients less than 40 years of age with a lumbar disc herniation.[29]

5. Pathophysiology of lumbar disc herniations

As patients age, there is a natural degenerative process of the intervertebral disc that may predispose the discs to injury, and these changes being within the first few years of life. By the age of three, there is a significant decrease in the number of capillaries extending from the endplate to the AF, changes in the cell morphology, and cell density within the NP, and small clefts formed in the AF.[30,31] While a multitude of studies have been designed to characterize every step in the degenerative process of the intervertebral disc as patients age, the changes to the AF may be particularly important in the development of intervertebral disc herniations. As

patients age, there is a steady increase in number and severity of annular clefts as well as clustering and apoptosis of fibroblast-like cells.[30,32] Furthermore, starting in the second decade of life the clear boundary between the AF and NP begins to slowly disappear.[3] Importantly, the outer layer of the AF is not affected until later in life,[3] and the integrity of the outer layer of the AF may help prevent disc herniations.

While a herniated disc is traditionally thought of as a herniation of the NP through the AF, histologic examination of surgical specimens has shown that a pure

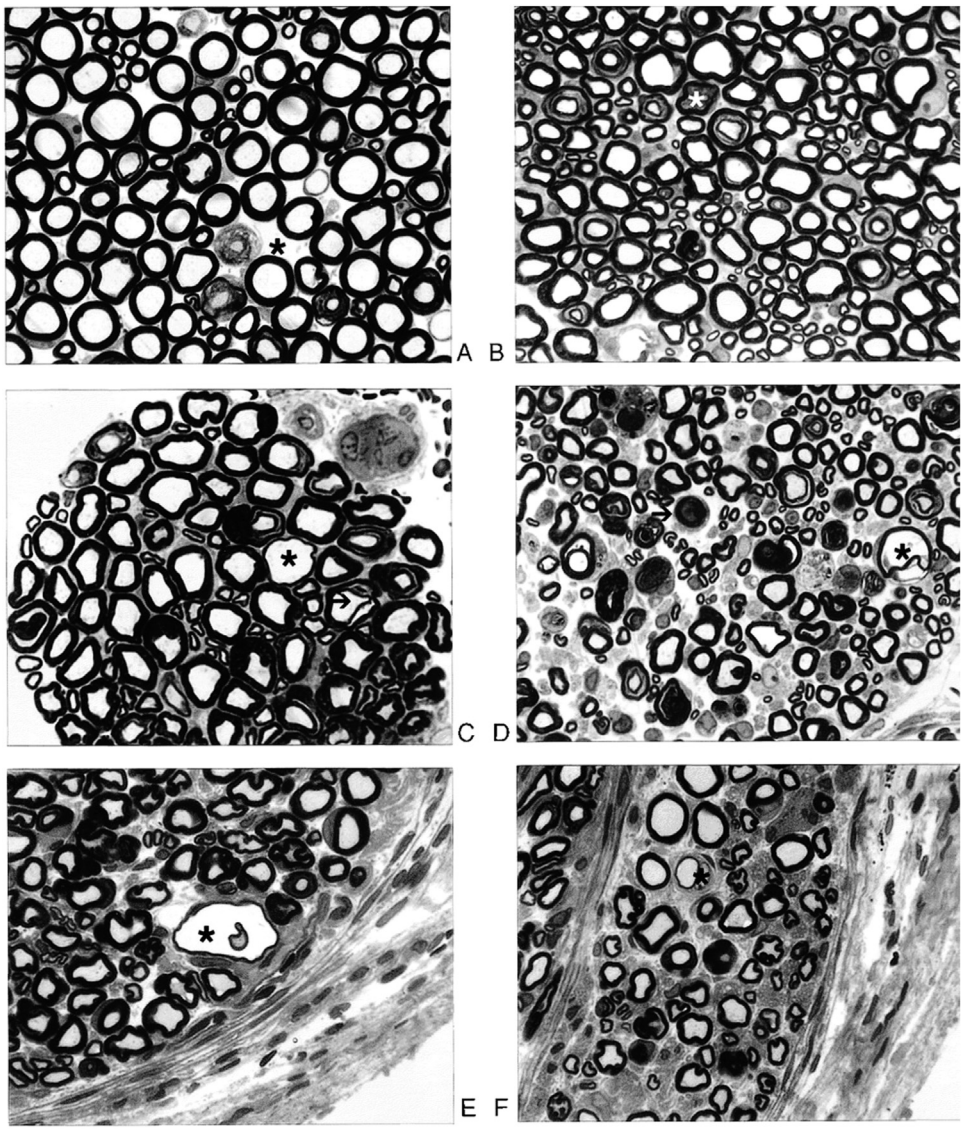

Fig. 3 – "Histologic sections of rat L5 nerve root exposed to tumor necrosis factor alpha (TNF alpha).[45] All the animals were treated similarly, but tissue was removed at the following times after TNF alpha application: day 1 (A), day 3 (B), day 5 (C), day 7 (D), day 28 (E and F). From plastic embedded specimens, 2 μm-thick sections were cut and stained with methylene blue Azure II. All magnification 400×. (A) Exposure to TNF alpha caused Schwann cell activation (evidenced as cytoplasmic hypertrophy), edema (evidenced as structureless space), and early changes in myelin integrity (*) within the first 24 h after TNF alpha exposure. (B) By day 3, Wallerian degeneration of nerve fibers is evident, seen here (*) as dark-staining axons and myelin blebbing. (C) The degenerative process continues with further blebbing of myelin and hydropic, swollen axoplasm (*). (C) Approximately 7 days after initial exposure to TNF alpha, the pathology is at its most severe level, with extensive Wallerian degeneration and demyelination evident in this illustration. Note numerous dark-staining axons, myelin blebbing, and active phagocytosis of degenerating nerve fibers. This phagocytosis is associated with activated macrophage invasion. A peculiar but characteristic feature of TNF alpha injury is splitting and expansion of the myelin sheaths (*). This may lead to either demyelination or Wallerian degeneration of the nerve fiber. (E) There is continuing degeneration of myelin evident even 28 days after TNF alpha exposure. (F) Remyelination, seen in this section, is characterized by thinly myelinated nerve fibers (*). Sections (E) and (F) both illustrate an increase in the density of collagen fibers both inside and outside the perineurium. Collagen stains red in these illustrations. This deposition is subsequent to TNF alpha-induced activation of fibroblasts, which can be seen to have proliferated in the spaces adjacent to the perineurium."

herniation of NP is rare. The annulus makes up a portion of the herniation in two-thirds of the cases, and approximately 20% of all herniations include a portion of the cartilaginous endplate.[3]

Lumbar disc herniations are most commonly posterolateral herniations that affect the traversing nerve root, and pain may either be from mechanical compression or chemical irritation of the nerve root. Mechanical compression can deform and stretch the nerve, as well as compress the microcirculation leading to ischemia and radicular symptoms; additionally, the herniation stimulates a substantial inflammatory cascade that is critical in the resorption of the disc herniation, but it can also lead to chemical irritation of the nerve root and radicular symptoms.[33–42]

The elevation of multiple cytokines including TNF alpha, interleukin-1 (IL1), fibroblast growth factor (FGF), intracellular adhesion molecule-1, lymphocyte function-associated antigen, midkine (MK), monocyte chemotactic protein-3 (MCP-3), monocyte chemotactic protein-4 (MCP-4), RANTES, and interferon gamma-induced protein-10 (IG-10) have all been identified after a lumbar disc herniation[33–42]; however, the role of only a few cytokines on intervertebral disc resorption and radicular symptoms has been fully identified. The concentration of FGF is elevated in surgical specimens of human lumbar disc herniations, and this cytokine potently attracts macrophages to the injury site.[33] Additionally, larger herniations such as extrusions and sequestrations have a significantly increased level of FGF compared to smaller protrusions. In a rabbit model, the increase in FGF concentration has been shown to be beneficial, as it leads to an increase in disc resorption.[39] Similarly MK is increased in herniated disc tissue, and in a similar model, MK has been shown to increase herniated disc resorption.[42]

While the inflammatory cascade is beneficial because it leads to resorption of the herniated discs, it also is partly responsible for the symptoms from a herniated disc. While there is little innervation to uninjured intervertebral discs, after being exposed to the inflammatory cascade, up to 80% of disc herniations have nerves present after being surgically removed.[3] Additionally, there is a significant increase in the concentration of TNF alpha in lumbar disc herniations compared to intact intervertebral discs,[43] and TNF alpha has been repeatedly demonstrated to stimulate radiculitis.[41,44–47] In a rat study, Igarashi et al.[45] demonstrated that the exogenous application of TNF alpha to lumbar nerve roots leads to behavioral changes in the rats similar to a lumbar herniated disc, and furthermore, histological changes in the nerve root such as edema in the endoneurial space, alteration to the myelin, and eventual Wallerian degeneration of portions of the nerve were observed (Fig. 3). Similarly, Genevay et al.[35] reported an increase in the TNF-alpha concentration in the epidural fat of patients with a herniated lumbar disc and radiculopathy compared to patients undergoing lumbar spine surgery without radicular symptoms.

6. Conclusion

The lumbar intervertebral disc is an avascular structure with limited regenerative capabilities that is required to withstand significant axial load, as well as flexion/extension, lateral bending, and rotational forces. Because of this, lumbar disc herniations are common. Multiple risk factors including family history, heavy lifting, and obesity have been identified, and the injury results in both mechanical compression of the nerve root as well as chemical irritation.

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