REVIEW ARTICLE

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Degenerative Cervical Spondylosis

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Degenerative cervical spondylosis is a chronic, progressive deterioration of osseocartilaginous components of the cervical spine that is most often related to aging. Radiographic evidence of degeneration of the cervical spine occurs in virtually all persons as they age; however, not all persons have the typical symptoms of neck pain or neurologic deficits that correspond to the mechanical compression of neural elements. Symptomatic cervical spondylosis is initially managed with nonsurgical treatment options, which usually result in abatement of symptoms. Surgical intervention may be indicated if there is clinically significant neurologic dysfunction or progressive instability or deformity of the cervical spine. No currently approved therapy addresses the cause of degenerative cervical spondylosis or reverses the deterioration. In select patients, surgical intervention can lead to favorable outcomes.

TERMINOLOGY AND EPIDEMIOLOGY

Degeneration of the cervical spine has acquired many equivalent names, including degenerative cervical spondylosis, cervical degenerative disease, cervical spondylosis, cervical osteoarthritis, and neck arthritis. The term spondylosis comes from the Greek word *spóndylos*, meaning vertebra. In general, these terms refer to age-related wear and tear that affect elements of the cervical spine over time, including the intervertebral disks, facet joints, and other connective-tissue structures (e.g., cervical spinal ligaments). However, cervical spine degeneration may also have immune inflammatory components.[1,2] The disorder may be associated with generalized neck pain, mechanical or axial neck pain, compression and inflammation of the cervical nerve roots exiting the cervical spine (cervical radiculopathy), and compression and inflammation of the adjacent cervical spinal cord (cervical myelopathy).[3]

Although age-related degenerative changes of the spine are almost universal, they may begin as early as in the first decade of life.[4] Population-based studies have shown that approximately 80 to 90% of people have disk degeneration on magnetic resonance imaging (MRI) by the age of 50 years.[5,6] A review of the global burden of low back and neck pain estimated that in 2015, more than a third of a billion people worldwide had mechanical neck pain of at least 3 months' duration,[7] underscoring the global health implications of degenerative cervical spondylosis.[8] A much smaller number of people have cervical radiculopathy (estimated annual incidence, approximately 83 cases per 100,000 persons)[9] and myelopathy (approximately 4 per 100,000)[10] as a result of cervical spondylosis. Clinical features of spondylosis are more common in men than in women, with a peak incidence between the ages of 40 and 60 years for both men and women.[11,12]

PATHOGENESIS AND PATHOPHYSIOLOGY

Although degenerative cervical spondylosis can affect any component of the cervical spine, such as bone quality and joint structures,[13] the most clinically significant changes occur in the intervertebral disks and facet joints. The intervertebral disk consists of the annulus fibrosus on the exterior border of the disk and the nucleus pulposus in the interior.[14] Like most dense connective tissue (e.g., ligaments), the intervertebral disk is essentially avascular.[15,16] Nutrient and waste exchange occur primarily through diffusion across the capillary beds in the adjacent superior and inferior vertebral end plates.[17] The intervertebral disks are metabolically active tissues, and cells deep within the disk, where oxygen is scarce, have adopted mechanisms to compensate for the relative hypoxia, including the up-regulation of hypoxia-inducible factors (e.g., HIF-1α).[18,19] Inner intervertebral disk cells (nucleopulpocytes) exist in a precarious state and may die in the presence of age-related changes such as vertebral bony end-plate calcification that decrease the limited exchange of nutrient and waste products.[17]

The loss of intervertebral disk cells is thought to contribute to a shift from tissue homeostasis toward net catabolism, leading to intervertebral disk deterioration.[20] However, the events triggering catabolic processes within the intervertebral disk have not been clearly defined. Such events may have a genetic basis or may be related to previous spinal trauma, including subclinical and unnoticed injuries.[21,22] Up-regulation of proinflammatory cytokines within the disk, including tumor necrosis factor α, interleukin-1β, and interleukin-6, occurs concomitantly with the loss of matrix-producing cells, further promoting the loss or senescence of native matrix-producing cells and subsequent replacement with fibroblast-like cells.[20] As a result, the production of hydrophilic proteoglycans is decreased, leading to gradual desiccation of the disk and the transfer of biomechanical loads from the nucleus pulposus to the surrounding annulus.[13] Furthermore, this degenerative process is accompanied by the secondary up-regulation of matrix metalloproteinases by resident disk cells, which lowers the yield strength of the annulus.[23] The combination of increased load sharing by the annulus and decreased yield strength predisposes the annulus to fissuring, with resultant herniation of the nucleus pulposus (the common condition of disk herniation), which impinges on the spinal cord or nerve roots.

In addition, disk desiccation is associated with loss of disk height, which is one reason that people "shrink" with age. Loss of disk height also narrows the foramina, through which nerve roots exit the spinal column, and leads to circumferential bulging of the annulus.

Finally, nociceptive nerve fibers that are present in the annulus and nucleus pulposus become sensitized by the cytokine milieu of the degenerative disk, putatively leading to a syndrome of pure diskogenic pain.[24,25] Mechanical neck pain is more often due to the distortion of surrounding soft tissues, including muscles and ligaments, and the cause of pain in patients with degenerative cervical spondylosis is often difficult to determine. It has been suggested that the central nervous system may become sensitized and perpetuate neck discomfort in patients with chronic spinal pain.[26,27]

Degeneration of the cervical facet joints, a set of two synovial joints that stabilize adjacent vertebrae at every spinal level below C1, may occur as a result of — or independent of — degeneration of the intervertebral disk. Such degeneration leads to pain and radiculopathy.

Myelopathy occurs if vertebral bodies are displaced, a condition termed spondylolisthesis.[4] This process is the result of damage to several elements of the spinal architecture. Normally, the cervical facet joints provide load-bearing support alongside the intervertebral disk and stabilize the neck during flexion, extension, and rotation. In the context of disk degeneration, the facet joints may be subjected to increased load bearing, which leads to osseocartilaginous alterations and destabilizes the joints.[13] Degeneration of the facet joints is similar to degeneration seen in other diarthrodial joints, such as the knee, and may be characterized by joint-space narrowing, subchondral sclerosis, and osteophyte formation. These changes narrow the spinal canal and neural foramina and decrease neck mobility. Like the intervertebral disk, the facet joints are innervated by nociceptive nerve fibers and may be sources of cervical spine pain.[28] Cervical facet joint syndrome, which is focal pain caused by degeneration of a cervical

Table 1. Worrisome Signs and Symptoms in the Evaluation of Patients with Degenerative Cervical Spondylosis.*

Signs and Symptoms	Cause	Physical Examination
History of cancer (especially breast, prostate, or lung), weight loss, night sweats, fever, nocturnal neck pain	Cancer	Variable findings, neurologic deficit, exquisite tenderness over vertebral body
History of intravenous drug use, immunocompromised status, fever, diabetes, recent sepsis	Spinal abscess	Usually severe local pain
Decreased dexterity in hands or feet, gait and balance instability, increased urinary frequency and urgency	Spondylitic myelopathy	Hyperreflexia, clonus, ataxia, Romberg's sign, atrophy of intrinsic hand muscles

* The information is from Childress and Becker.[31]

facet joint, is recognized by some clinicians as a subcategory of degenerative cervical spondylosis that calls for distinct treatment.[29,30]

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with degenerative cervical spondylosis may present with mechanical neck pain, radiculopathy, myelopathy, or a combination of these symptoms. Mechanical neck pain may be isolated to the neck or may radiate broadly, such as to the shoulders, head, chest, and back. The source of the pain is often difficult for patients to pinpoint. This complicates management, since the pain could stem from the degenerated intervertebral disk (pure diskogenic pain), the degenerated facet joints, or the muscular and ligamentous structures. The pain is often worsened by neck motion and relieved by rest and immobilization. However, neck pain is relatively common in the general population, affecting an estimated 15% of people at any time, and is not specific to degenerative cervical spondylosis.[3] A patient presenting with neck pain may be asked about red-flag signs and symptoms, such as a history of cancer, gait instability or sensory loss associated with myelopathy, and fever with nocturnal pain suggestive of spinal abscess — all of which require rapid evaluation (Table 1).

Cervical radiculopathy from spondylosis is caused by mechanical compression and inflammation of a cervical nerve root, most commonly C6 or C7.[31,32] The compression may be acute (e.g., caused by an abruptly herniated disk) or chronic (e.g., the result of hypertrophied facet joints). Pain arising from the compressed and inflamed nerve root, mainly radiating from the shoulder or upper back to the proximal arm, is the most common symptom of cervical degenerative radiculopathy.[9] Radicular neck pain may also be accompanied by painful neck spasms. Patients with cervical degenerative radiculopathy may have paresthesia, numbness, or weakness that often — but not always — corresponds to dermatomal distributions of the affected cervical nerve root.[31] Diminished deep-tendon reflexes, such as those of the biceps (C6 nerve root) or triceps (C7 nerve root), are corroborative of nerve-root compression.

Provocative tests used to aid in the diagnosis of cervical degenerative radiculopathy include the Spurling test, the shoulder-abduction test, and the cervical-traction test.[33,34] In the typical application of the Spurling test, the patient's neck is turned to the side of the radicular pain and is then slightly extended. Downward pressure is applied to the top of the patient's head, which narrows the neural foramina on the affected side. If the pain is elicited or worsened, it can be attributed to radiculopathy. The test may be repeated by turning the patient's head to the side opposite the pain; if the pain is worsened by this maneuver, a musculoskeletal cause is suggested. The shoulder-abduction test is another useful diagnostic tool. This test is performed by placing the palm or forearm of the affected arm on top of the patient's head. If the radicular pain is relieved, radiculopathy is the likely source of the pain. Manual cervical traction may be used as a test to expand the neural foramina; if radicular pain is relieved in this way, then radiculopathy is suggested.

Cervical degenerative myelopathy is the least common but most worrisome presentation of degenerative cervical spondylosis. It is caused by

Table 2. Differential Diagnosis for Cervical Degenerative Spondylosis.*

Clinical Feature	Acute Conditions	Chronic Conditions
Neck pain	Cervical strain or sprain, painful intervertebral disk, painful facet joint	Fibromyalgia, failed surgical fusion, referred visceral pain, hypochondriasis and somatoform disorders
Radiculopathy	Intervertebral disk herniation, brachial plexitis	Intervertebral disk herniation, shoulder disorder, entrapment neuropathy, focal facet hypertrophy
Myelopathy	Intervertebral disk herniation, pathologic fracture, Guillain–Barré syndrome	Intervertebral disk herniation, spinal instability, central canal stenosis, multiple sclerosis, neoplasm, infection, myopathies, syringomyelia, arteriovenous malformation, vitamin B_{12} deficiency

* The information is from Voorhies.[3]

mechanical compression and is associated with inflammation and edema of the spinal cord; inflammation and edema lead to slow, progressive deterioration of neurologic function as a result of narrowing of the spinal canal and compression of the long tracts and local segmental elements of the spinal cord.[35] Both static (at rest) and dynamic (repetitive motion) compressive factors contribute to deterioration.[36,37] For example, an already compressed spinal cord may sustain further compression on neck flexion, which increases tension on the spinal cord because of its relatively fixed longitudinal position, maintained by the dentate ligaments and cervical nerve roots. Patients with myelopathy may present with a variety of subtle neurologic findings, which they may attribute to natural loss of function with age. These include loss of manual dexterity; gait and balance disturbances, especially in the absence of visual cues (Romberg's sign); sensory loss in the hands or feet; arm or hand weakness; and defecatory or urinary frequency, urgency, or hesitancy. There may be upper-motor-neuron signs, including clonus, hyperreflexia, Hoffmann's sign, and Babinski's sign.[38] Patients with symptoms of myelopathy almost always have associated neck pain and stiffness and may have pain in the arms or shoulders. Radicular features, mentioned above, are also common in the context of cervical degenerative myelopathy. Some persons have Lhermitte's sign (electrical sensations radiating down the spine or across the shoulders) on neck flexion, and other signs and symptoms that are occasionally attributable to cervical myelopathy but have many alternative causes.[38]

Table 2 outlines the differential diagnosis for the main presentations of cervical spondylosis, with or without myelopathy.[3,31,39] In evaluating patients with neck pain, it is useful to recognize that virtually all patients older than 50 years of age have cervical degenerative changes on one or more forms of imaging, and many findings are not specific. For these reasons, diagnostic imaging is often not recommended for patients who initially present with nontraumatic neck pain without neurologic symptoms or signs or red flags.

For patients with persistent neck, shoulder, or arm pain and suspected radiculopathy, an initial radiographic evaluation may be performed, with the use of anteroposterior, lateral, and oblique radiographs, which are relatively inexpensive and provide information pertaining to degenerative changes and alignment.[40] Lateral flexion or extension views may also be obtained during the initial evaluation and may disclose cervical instability, limited range of motion, and fused cervical spine segments.[41] For patients with progressive neurologic impairments or any feature that suggests myelopathy, cervical spine MRI without the administration of contrast material is the preferred imaging technique, since it provides information about osseous, soft-tissue, and spinal cord structures (Fig. 1).[42] The presence of an abnormal signal within the cervical cord or adjacent to the level of compression by spondylosis is considered a serious finding, which may signify a less satisfactory outcome with surgical decompression than would otherwise be expected. On the other hand, in some cases the spinal cord seems able to withstand a substantial degree of deformation, with few resulting symptoms, if the deformation develops slowly. The decision to surgically decompress the spinal canal in cases of cervical spondylosis incorporates, but does not entirely depend on, such factors as the degree of disability (e.g., impairment of activities of daily living) and the rapidity of symptom progression. If MRI is con-

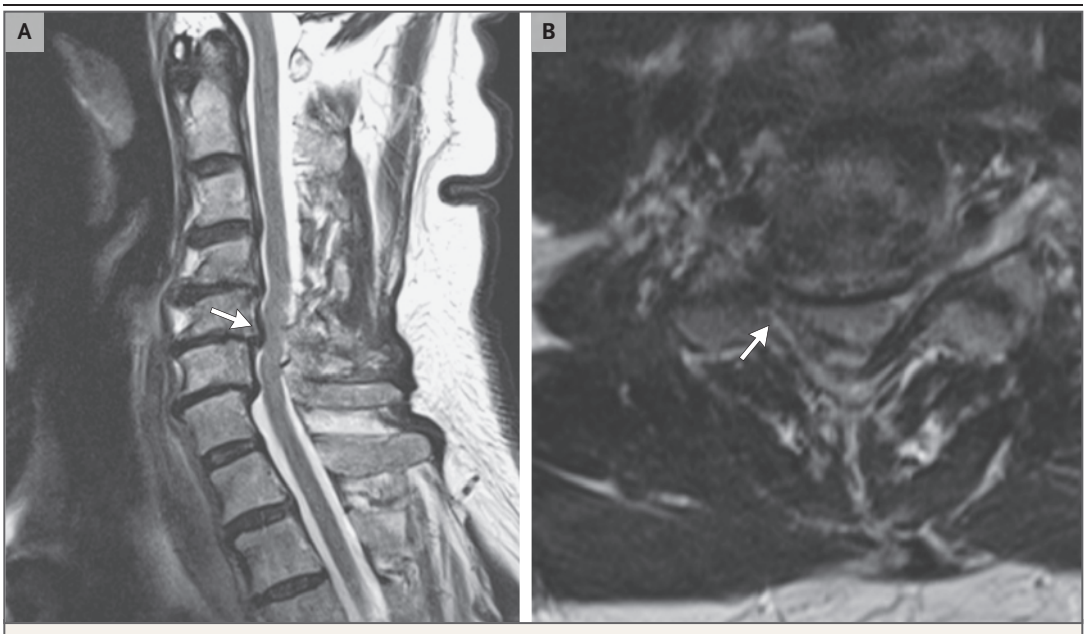


Figure 1. MRI Scans of the Cervical Spine in a Patient with Cervical Spondylosis.

A 75-year-old man presented with a 2-year history of progressive upper-extremity paresthesias and radicular pain. He reported having dropped items recently from both hands and noted dexterity and balance deficits but no bowel or bladder incontinence. A sagittal T2-weighted MRI scan shows stenosis of the central spinal canal at C4–C7, with an osteophyte, deformation of the cord, disk material, and spondylolisthesis at C5–C6 (Panel A, arrow). An axial T2-weighted image shows severe foraminal stenosis (Panel B, arrow) and severe encroachment on the spinal canal by osteophyte, ligamentous, and facet hypertrophy.

traindicated or unavailable, a computed tomographic (CT) study or CT myelography of the cervical spine (Fig. 2) is an alternative imaging approach.[43,44] Electrodiagnostic testing may be helpful in evaluating cervical radiculopathy by showing denervation in muscles specifically referable to a single cervical nerve root.[45,46] Guidelines for the use of injections and other approaches, including advanced imaging studies such as single-photon emission CT to identify "pain generators," are ill defined and lack evidence-based support.[3,47,48]

TREATMENT APPROACHES AND OUTCOMES

Various treatment algorithms have been created for managing degenerative cervical spondylosis and mechanical neck pain, radiculopathy, or myelopathy.[31,49-51] The management of degenerative neck pain in patients who have no neurologic deficit is typically a "tincture of time," along with analgesics and other conservative options, including physical therapy.[3] Some patients have worsening or chronic pain, even in the absence of signs of nerve-root or spinal cord compression. The care of patients with chronic, degenerative neck pain can be challenging and frustrating for both patient and health care provider, especially given the difficulty in identifying the cause. Many patients benefit from a referral to a specialist in chronic pain management, and many have improvement when coexisting psychiatric disorders, including anxiety and depression, are treated.[52-54] In general, surgical outcomes for patients with chronic neck pain are limited, especially when the source of the pain cannot be identified.

Most patients with degenerative cervical radiculopathy have reduced pain and improved neurologic function with nonsurgical care, including oral analgesics, epidural glucocorticoid injections, physical therapy, cervical traction or brief immobilization in a cervical orthosis, and other options, such as massage.[9,31,55] Few high-quality studies have evaluated these conservative therapies to provide a recommendation, and the various approaches may offer similar rates of symptomatic improvement.

The severity and rate of progression of neuro-

logic deficits are the main aspects of the evaluation of patients with degenerative cervical radiculopathy, since clinically significant motor weakness or worsening neurologic symptoms usually indicate the need for surgical evaluation. The timing for surgical evaluation is not clear, although advancing nerve-root compression in association with weakness, atrophy, or sensory loss, in addition to deteriorating neurologic status at any time, generally prompts referral to a spine surgeon. In patients with identifiable causes of nerve-root compression — for example, a herniated disk — surgical outcomes are often good.[56]

Patients with degenerative cervical myelopathy are also typically referred to a spine surgeon.

Figure 3 (facing page). Cervical Spine Decompression and Fusion.

Anterior cervical diskectomies at C3–C4 and C4–C5, with the placement of bone-graft spacers where disks were removed and stabilizing screw–plate instrumentation, are shown schematically in Panel A and in a lateral radiograph in Panel C. Posterior laminectomies and lateral mass screw–rod instrumentation and fusion at C3–C6 are shown schematically in Panel B and in an anteroposterior radiograph in Panel D.

In view of the progressive natural history of nerve-root or spinal cord compression or pain in most patients, surgical treatment for degenerative cervical myelopathy can be a good option.[35,36] For patients with moderate-to-severe

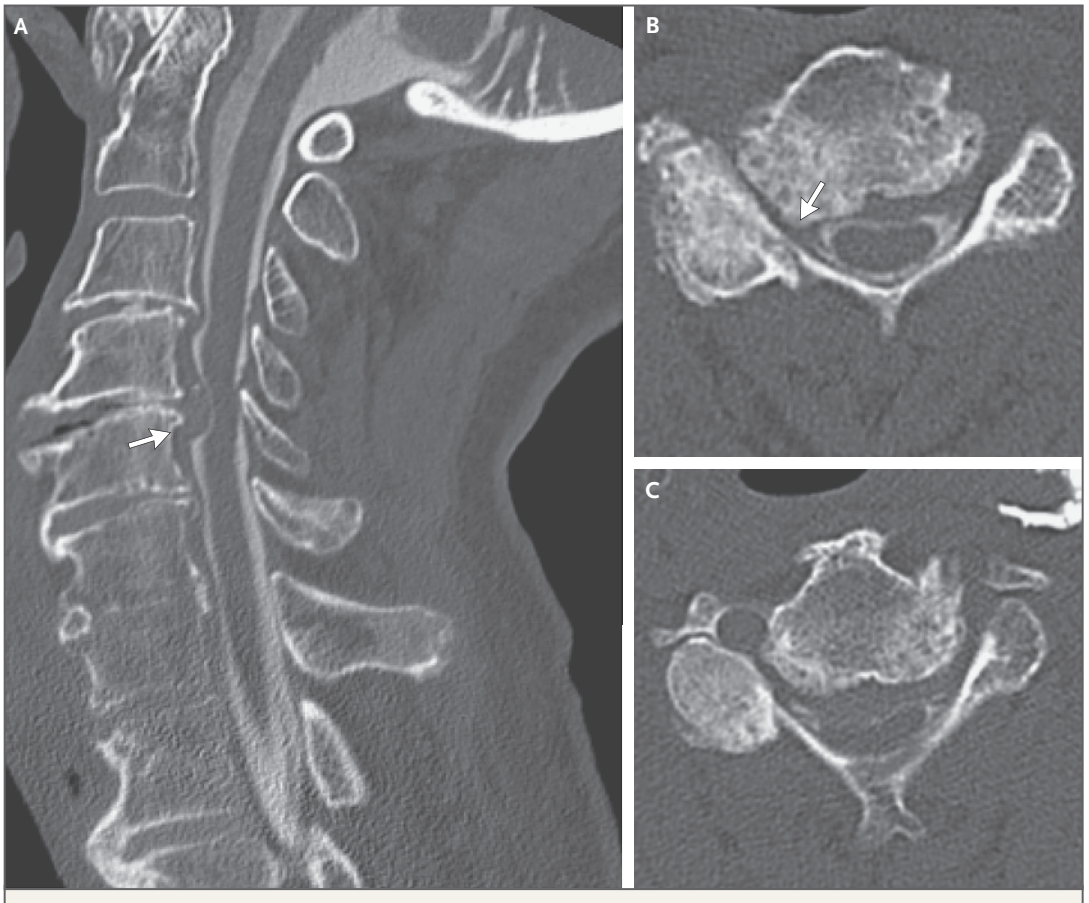
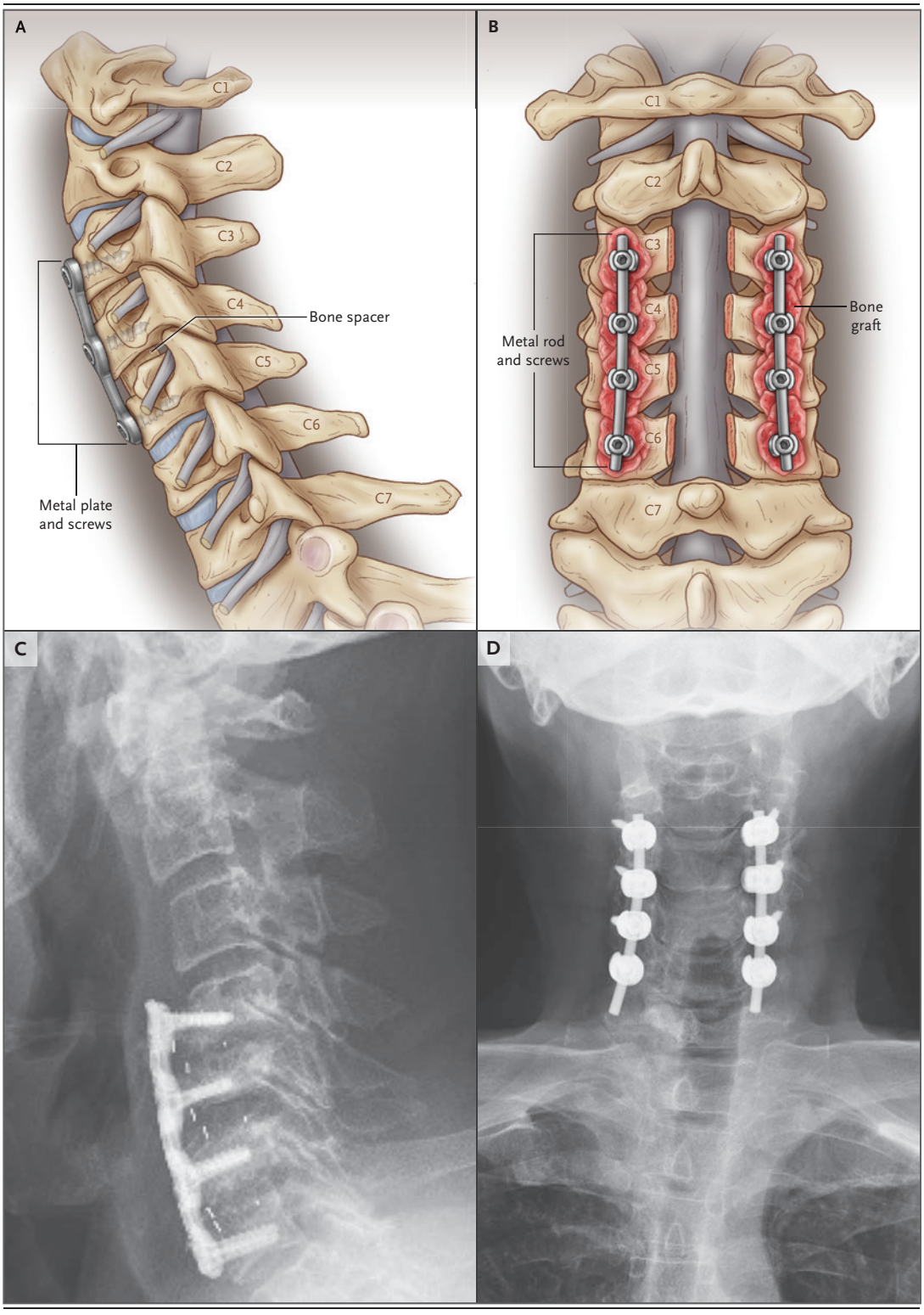


Figure 2. Postmyelography CT Scans of the Cervical Spine.

A 68-year-old woman had increasing hand weakness, intrinsic hand-muscle atrophy, and hand numbness. She had begun falling and had Romberg's sign. She was unable to undergo MRI. A midsagittal CT myelogram (Panel A) shows multilevel cervical spondylosis with osteophytes, disk protrusion, and cord compression at C4–C5 (arrow). An axial image at the C3–C4 disk space shows a right lateral osteophyte (Panel B, arrow) encroaching on the neural foramen, and a similar image at the C4–C5 disk space shows marked cord compression (Panel C).



neurologic deficits, consensus statements have suggested that nonsurgical management, as compared with surgery, leads to inferior clinical outcomes. However, data from well-performed randomized trials, such as those that have been conducted for lumbar spine disease, are lacking, and so this suggestion is driven largely by clinical experience.[57]

Surgical approaches to the treatment of degenerative cervical radiculopathy, myelopathy, or both include anterior, posterior, and anteroposterior techniques (Fig. 3).[58-60] Each technique has its proponents and inherent drawbacks, related mainly to the adequacy of decompression of the spinal cord and nerve roots, maintenance of stability of the spinal column, duration of the procedure and blood loss, and time required to recover from surgery and be discharged from the hospital. In some instances, the surgeon's facility and experience with a certain procedure are considerations in choosing the approach. The goals of surgery are to decompress the nerve roots or spinal cord and stabilize the spine, while attempting to restore or maintain relatively normal spinal alignment. Outcomes depend on the severity and duration of the neurologic deficit at the time of surgery. Advanced age, smoking, and coexisting conditions such as obesity and diabetes mellitus have been shown to negatively affect outcomes.[61]

PREVENTION

In general, virtually all people have some degree of cervical degeneration with age, including intervertebral disk desiccation, neural foraminal narrowing, osteophyte formation, and facet joint hypertrophy. Why only some patients have symptoms after these changes occur is unclear. Certain anatomical configurations, such as a congenitally narrow spinal canal, short pedicles, and small neural foramina, are almost certainly contributors to the development of symptoms for a given degree of spondylosis. Staying physically active, maintaining good posture, and preventing neck injuries may all help prevent symptomatic degenerative cervical spondylosis. In addition, smoking and obesity have been found to be associated with spondylosis; therefore, managing these risk factors may offer benefits.[62]

CONCLUSIONS AND RECOMMENDATIONS

Degenerative cervical spondylosis is caused by arthritic changes in the osseocartilaginous components of the cervical spine, which may compress spinal nerve roots, the spinal cord, or both, causing neck pain, radiculopathy, or myelopathy. Treatment is generally nonsurgical, especially for pain and mild radiculopathy, which are typically self-limiting. However, surgery is generally indicated to treat myelopathy and may be indicated for persistent and severe nerve-root compression.

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REFERENCES

1. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013;21:16-21.
2. Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis. Clin Immunol 2013;146:185-96.
3. Voorhies RM. Cervical spondylosis: recognition, differential diagnosis, and management. Ochsner J 2001;3:78-84.
4. Benoist M. Natural history of the aging spine. Eur Spine J 2003;12:Suppl 2:S86-S89.
5. Brinjikji W, Luetmer PH, Comstock B, et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. AJNR Am J Neuroradiol 2015;36:811-6.
6. Teraguchi M, Yoshimura N, Hashizume H, et al. Prevalence and distribution of intervertebral disc degeneration over the entire spine in a population-based cohort: the Wakayama Spine Study. Osteoarthritis Cartilage 2014;22:104-10.
7. Hurwitz EL, Randhawa K, Yu H, Côté P, Haldeman S. The Global Spine Care Initiative: a summary of the global burden of low back and neck pain studies. Eur Spine J 2018;27:Suppl 6:796-801.
8. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743-800.
9. Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervi-

cal radiculopathy: a population-based study from Rochester, Minnesota, 1976 through 1990. Brain 1994;117:325-35.
10. Wu JC, Ko CC, Yen YS, et al. Epidemiology of cervical spondylotic myelopathy and its risk of causing spinal cord injury: a national cohort study. Neurosurg Focus 2013;35(1):E10.
11. Kelly JC, Groarke PJ, Butler JS, Poynton AR, O'Byrne JM. The natural history and clinical syndromes of degenerative cervical spondylosis. Adv Orthop 2012; 2012:393642.
12. Lv Y, Tian W, Chen D, Liu Y, Wang L, Duan F. The prevalence and associated factors of symptomatic cervical spondylosis in Chinese adults: a community-based cross-sectional study. BMC Musculoskelet Disord 2018;19:325.
13. Ferrara LA. The biomechanics of cervical spondylosis. Adv Orthop 2012;2012: 493605.
14. Zaidi HA, Theodore N. Diskectomy. In: Aminoff MJ, Daroff RB, eds. Encyclopedia of the neurological sciences. 2nd ed. Oxford, England: Academic Press, 2014: 1009-10.
15. Grunhagen T, Shirazi-Adl A, Fairbank JC, Urban JP. Intervertebral disk nutrition: a review of factors influencing concentrations of nutrients and metabolites. Orthop Clin North Am 2011;42:465-77.
16. Nerlich AG, Schaaf R, Wälchli B, Boos N. Temporo-spatial distribution of blood vessels in human lumbar intervertebral discs. Eur Spine J 2007;16:547-55.
17. van der Werf M, Lezuo P, Maissen O, van Donkelaar CC, Ito K. Inhibition of vertebral endplate perfusion results in decreased intervertebral disc intranuclear diffusive transport. J Anat 2007;211:769-74.
18. Risbud MV, Schipani E, Shapiro IM. Hypoxic regulation of nucleus pulposus cell survival: from niche to notch. Am J Pathol 2010;176:1577-83.
19. Semenza GL. Hypoxia-inducible factor 1 (HIF-1) pathway. Sci STKE 2007;407: cm8.
20. Feng C, Liu H, Yang M, Zhang Y, Huang B, Zhou Y. Disc cell senescence in intervertebral disc degeneration: causes and molecular pathways. Cell Cycle 2016; 15:1674-84.
21. Feng Y, Egan B, Wang J. Genetic factors in intervertebral disc degeneration. Genes Dis 2016;3:178-85.
22. Theodore N, Ahmed AK, Fulton T, et al. Genetic predisposition to symptomatic lumbar disk herniation in pediatric and young adult patients. Spine (Phila Pa 1976) 2019;44(11):E640-E649.
23. Roberts S, Caterson B, Menage J, Evans EH, Jaffray DC, Eisenstein SM. Matrix metalloproteinases and aggrecanase: their role in disorders of the human intervertebral disc. Spine (Phila Pa 1976) 2000;25: 3005-13.
24. Binch AL, Cole AA, Breakwell LM, et al. Nerves are more abundant than blood vessels in the degenerate human intervertebral disc. Arthritis Res Ther 2015; 17:370.
25. García-Cosamalón J, del Valle ME, Calavia MG, et al. Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain? J Anat 2010;217: 1-15.
26. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. Eur J Pain 2007;11: 415-20.
27. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152:Suppl:S2-S15.
28. Inami S, Shiga T, Tsujino A, Yabuki T, Okado N, Ochiai N. Immunohistochemical demonstration of nerve fibers in the synovial fold of the human cervical facet joint. J Orthop Res 2001;19:593-6.
29. Manchikanti L, Boswell MV, Singh V, Pampati V, Damron KS, Beyer CD. Prevalence of facet joint pain in chronic spinal pain of cervical, thoracic, and lumbar regions. BMC Musculoskelet Disord 2004;5: 15.
30. Perolat R, Kastler A, Nicot B, et al. Facet joint syndrome: from diagnosis to interventional management. Insights Imaging 2018;9:773-89.
31. Childress MA, Becker BA. Nonoperative management of cervical radiculopathy. Am Fam Physician 2016;93:746-54.
32. Bono CM, Ghiselli G, Gilbert TJ, et al. An evidence-based clinical guideline for the diagnosis and treatment of cervical radiculopathy from degenerative disorders. Spine J 2011;11:64-72.
33. Ghasemi M, Golabchi K, Mousavi SA, et al. The value of provocative tests in diagnosis of cervical radiculopathy. J Res Med Sci 2013;18:Suppl 1:S35-S38.
34. Rubinstein SM, Pool JJ, van Tulder MW, Riphagen II, de Vet HC. A systematic review of the diagnostic accuracy of provocative tests of the neck for diagnosing cervical radiculopathy. Eur Spine J 2007; 16:307-19.
35. Emery SE. Cervical spondylotic myelopathy: diagnosis and treatment. J Am Acad Orthop Surg 2001;9:376-88.
36. Karadimas SK, Erwin WM, Ely CG, Dettori JR, Fehlings MG. Pathophysiology and natural history of cervical spondylotic myelopathy. Spine (Phila Pa 1976) 2013; 38:Suppl 1:S21-S36.
37. Liu S, Lafage R, Smith JS, et al. Impact of dynamic alignment, motion, and center of rotation on myelopathy grade and regional disability in cervical spondylotic myelopathy. J Neurosurg Spine 2015;23: 690-700.
38. Bakhsheshian J, Mehta VA, Liu JC. Current diagnosis and management of cervical spondylotic myelopathy. Global Spine J 2017;7:572-86.
39. Kim HJ, Tetreault LA, Massicotte EM, et al. Differential diagnosis for cervical spondylotic myelopathy: literature review. Spine (Phila Pa 1976) 2013;38:Suppl 1: S78-S88.
40. Green C, Butler J, Eustace S, Poynton A, O'Byrne JM. Imaging modalities for cervical spondylotic stenosis and myelopathy. Adv Orthop 2012;2012:908324.
41. Rao RD, Currier BL, Albert TJ, et al. Degenerative cervical spondylosis: clinical syndromes, pathogenesis, and management. Instr Course Lect 2008;57:447-69.
42. Nouri A, Martin AR, Mikulis D, Fehlings MG. Magnetic resonance imaging assessment of degenerative cervical myelopathy: a review of structural changes and measurement techniques. Neurosurg Focus 2016;40(6):E5.
43. Shafaie FF, Wippold FJ II, Gado M, Pilgram TK, Riew KD. Comparison of computed tomography myelography and magnetic resonance imaging in the evaluation of cervical spondylotic myelopathy and radiculopathy. Spine (Phila Pa 1976) 1999;24:1781-5.
44. Song KJ, Choi BW, Kim GH, Kim JR. Clinical usefulness of CT-myelogram comparing with the MRI in degenerative cervical spinal disorders: is CTM still useful for primary diagnostic tool? J Spinal Disord Tech 2009;22:353-7.
45. Callaghan BC, Burke JF, Feldman EL. Electrodiagnostic tests in polyneuropathy and radiculopathy. JAMA 2016;315:297-8.
46. Pawar S, Kashikar A, Shende V, Waghmare S. The study of diagnostic efficacy of nerve conduction study parameters in cervical radiculopathy. J Clin Diagn Res 2013;7:2680-2.
47. Cohen SP, Hooten WM. Advances in the diagnosis and management of neck pain. BMJ 2017;358:j3221.
48. Ravindra VM, Mazur MD, Bisson EF, Barton C, Shah LM, Dailey AT. The usefulness of single-photon emission computed tomography in defining painful upper cervical facet arthropathy. World Neurosurg 2016;96:390-5.
49. Binder AI. Cervical spondylosis and neck pain. BMJ 2007;334:527-31.
50. Fehlings MG, Tetreault LA, Riew KD, et al. A clinical practice guideline for the management of patients with degenerative cervical myelopathy: recommendations for patients with mild, moderate, and severe disease and nonmyelopathic patients with evidence of cord compression. Global Spine J 2017;7:Suppl:70S-83S.

51. Kjaer P, Kongsted A, Hartvigsen J, et al. National clinical guidelines for non-surgical treatment of patients with recent onset neck pain or cervical radiculopathy. Eur Spine J 2017;26:2242-57.
52. Lin SY, Sung FC, Lin CL, Chou LW, Hsu CY, Kao CH. Association of depression and cervical spondylosis: a nationwide retrospective propensity score-matched cohort study. J Clin Med 2018; 7(11):E387.
53. Stoffman MR, Roberts MS, King JT Jr. Cervical spondylotic myelopathy, depression, and anxiety: a cohort analysis of 89 patients. Neurosurgery 2005;57:307-13.
54. Tetreault L, Nagoshi N, Nakashima H, et al. Impact of depression and bipolar disorders on functional and quality of life outcomes in patients undergoing surgery for degenerative cervical myelopathy: analysis of a combined prospective dataset. Spine (Phila Pa 1976) 2017;42:372-8.
55. Fritz JM, Thackeray A, Brennan GP, Childs JD. Exercise only, exercise with mechanical traction, or exercise with overdoor traction for patients with cervical radiculopathy, with or without consideration of status on a previously described subgrouping rule: a randomized clinical trial. J Orthop Sports Phys Ther 2014;44: 45-57.
56. Gutman G, Rosenzweig DH, Golan JD. Surgical treatment of cervical radiculopathy: meta-analysis of randomized controlled trials. Spine (Phila Pa 1976) 2018; 43(6):E365-E372.
57. Fehlings MG, Wilson JR, Yoon ST, Rhee JM, Shamji MF, Lawrence BD. Symptomatic progression of cervical myelopathy and the role of nonsurgical management: a consensus statement. Spine (Phila Pa 1976) 2013;38:Suppl 1:S19-S20.
58. Buell TJ, Buchholz AL, Quinn JC, Shaffrey CI, Smith JS. Importance of sagittal alignment of the cervical spine in the management of degenerative cervical myelopathy. Neurosurg Clin N Am 2018;29: 69-82.
59. Cuellar J, Passias P. Cervical spondylotic myelopathy: a review of clinical diagnosis and treatment. Bull Hosp Jt Dis (2013) 2017;75:21-9.
60. Kavanagh RG, Butler JS, O'Byrne JM, Poynton AR. Operative techniques for cervical radiculopathy and myelopathy. Adv Orthop 2012;2012:794087.
61. Tetreault L, Palubiski LM, Kryshtalskyj M, et al. Significant predictors of outcome following surgery for the treatment of degenerative cervical myelopathy: a systematic review of the literature. Neurosurg Clin N Am 2018;29(1):115-127.e35.
62. Kadow T, Sowa G, Vo N, Kang JD. Molecular basis of intervertebral disc degeneration and herniations: what are the important translational questions? Clin Orthop Relat Res 2015;473:1903-12.

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