5 Pathobiology of Cervical Radiculopathy and Myelopathy

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Introduction

Symptomatic cervical spine disease commonly presents with signs and symptoms of radiculopathy and/or myelopathy. Understanding the pathobiologic mechanisms underlying radiculopathy and myelopathy is vital for appropriate and timely diagnosis and management. This chapter is an overview of current understanding of the pathophysiology of these two processes as it relates to their clinical presentation.

Cervical Radiculopathy

Cervical radiculopathy is the lower motor neuron and/or sensory manifestation of neurologic dysfunction in the distribution of a given cervical nerve root. While the true incidence of cervical radiculopathy is not known, a population-based study in Rochester, MN, from 1976 to 1990, showed an annual incidence of 107.3 per 100,000 men with a mean age of 47.6 and 63.5 per 100,000 females with a mean age of 48.2 [36]. Peak age-specific annual incidence was 202.9 per 100,000 people ages 50–54 [36]. More recently, Schoenfeld et al. found an incidence of cervical radiculopathy in the military population of 1.79 per 1000 person-years from 2000 to 2009 [39]. Risks factors in patients to develop cervical radiculopathy include axial load bearing, high-risk occupation (meat carriers, dentists, professional drivers), cigarette smoking, and prior lumbar radiculopathy [38]. Additional potentially implicated factors are prior cervical trauma, gender, race, and genetics [38]. Non-risk factors include repeated turning of the neck, sports, and sedentary occupations [38].

Cervical Radiculopathy Pathophysiology

The pathophysiology of degenerative cervical radiculopathy relates to age-related changes that occur within the intervertebral disc. Normally, the cervical intervertebral disc is characterized by a greater ventral disc height relative to dorsal, which is what contributes to the overall lordosis of this region. The annulus fibrosis of the ventral aspect contains multi-laminated, interweaving collagenous fibers of altering orientation; however the dorsal aspect is made of a thin layer of collagen [32]. With aging, however, the intervertebral disc diminishes the ability to retain water leading to decreased elasticity. This decrease in elasticity causes the disc to prolapse posteriorly, which can lead to compression of adjoining

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M. G. Kaiser et al. (eds.), *Degenerative Cervical Myelopathy and Radiculopathy*,
https://doi.org/10.1007/978-3-319-97952-6_5

neural structures, radiculopathy and/or myelopathy, and concomitant loss of cervical lordosis.

Static Mechanical Compression-Induced Radiculopathy

A Rochester population-based study demonstrated that 21.9% of patients with cervical radiculopathy present with a cervical disc protrusion and 68.4% with degenerative cervical spondylosis, which may lead to static compression of the nerve root [36]. Less common presentations of compressive cervical radiculopathies include spinal neoplasm and infection [40]. The mechanism of symptomatic compressive radiculopathy is not fully understood; however, there are likely multiple contributing factors. One proposed etiology is direct mechanical compression of the nerve root including the dorsal root ganglia, which may be acute or chronic in nature. Acute compression is often secondary to herniated nucleus pulposus (Fig. 5.1), whereas chronic compression is commonly due to slowly progressive degenerative disc-osteophyte complex formation (Fig. 5.2) with superimposed facet and/or uncovertebral hypertrophy (Fig. 5.3). Compression of the nerve root proximal to the dorsal root ganglion (DRG) causes increased endoneurial fluid pressure and decreased blood flow to the DRG [52], leading to neuronal ischemic injury [52]. Patients with cervical radiculopathy have sensory axonal

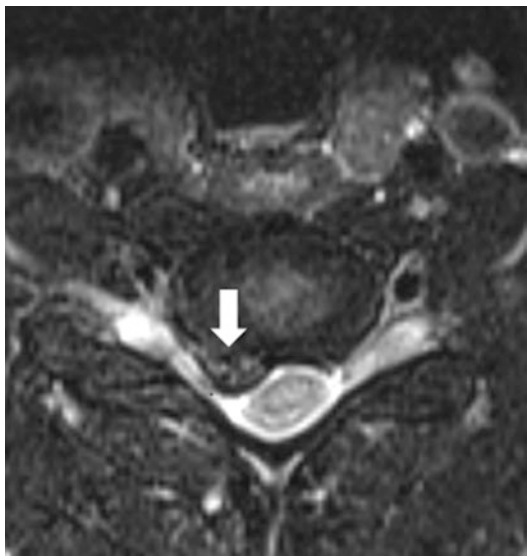

Fig. 5.1 MRI demonstrating an acute herniated nucleus pulposus (*arrow*) causing nerve root compression. The increased T2 signal within the paracentral disc herniation suggests an acute process

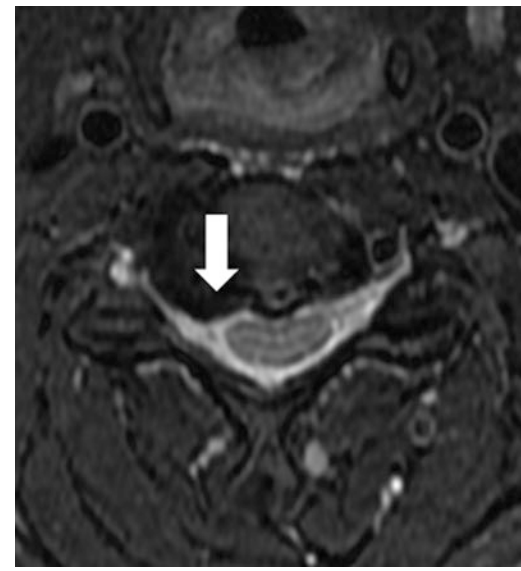

Fig. 5.2 MRI demonstrating a chronic disc-osteophyte complex (*arrow*) causing nerve root compression. The decreased T2 signal within the disc protrusion suggests a chronic process with likely possible osteophyte formation

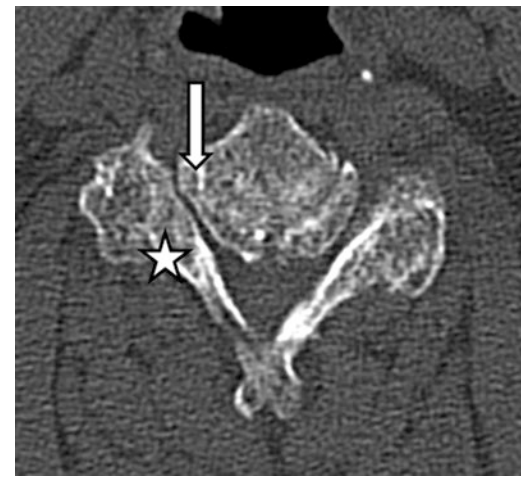

Fig. 5.3 CT demonstrating facet hypertrophy (star) and uncovertebral joint hypertrophy (*arrow*) causing neural foraminal stenosis and radiculopathy

dysfunction due to distal nerve axonal hyperpolarization thought to be due to Na+ -K+ ATPase over activation induced by proximal ischemia or remyelination of the axons [46]. Animal studies have revealed histologic, electrophysiologic, and functional changes in the nerve root as a result of chronic mechanical compression. Compressed nerve roots demonstrate thickened dura mater and arachnoid membrane with alterations in the blood-nerve barrier at 1 month, decreased number of large myelinated fibers at 3 months, and endoneurial fibrosis with Wallerian degeneration of nerve fibers at 6 months [53]. Jancalek and Dubovy showed a decreased number of myelinated axons in as little as 1 week of mechanical nerve compression [24]. Further, chronic compression of the dorsal root ganglia causes functional changes including enhanced excitability of sensory neurons, ectopic neuronal discharge, and hyperalgesia [44, 59].

Dynamic Compression-Induced Radiculopathy

Change in spinal alignment associated with cervical flexion, extension, and lateral bending may further cause dynamic compression or tension injury to cervical nerve roots. Rhee et al. report that the normal trajectory of nerve roots as they exit the cervical spine is at a 45° anterolateral angle toward the foramina, which may be subject to pathophysiologic stretch over ventral pathology with motion [37]. This repetitive dynamic compression may contribute to injury of the nerve root with associated radiculopathy over time.

Biochemical-Induced Radiculopathy

In addition to static and dynamic compression injury to the nerve, biochemical mediators released by the cervical disc also may have an important role in symptomatic radiculopathy. Burke et al. showed production of pro-inflammatory cytokines IL-6 and IL-8 from herniated nucleus pulposus in patients presenting with radiculopathy [8]. Release of TNF alpha causes upregulation of IL-1beta and nerve growth factor leading to hyperalgesia [50, 51]. Compared to normal disc material, herniated nucleus pulposus produces increased matrix metalloproteinases (MMP), nitric oxide, prostaglandin E2, and IL-6 [26, 60]. This pro-inflammatory chemical cascade is associated with increased pain and sensitization in the given nerve root distribution [50]. Compounding matters, it is thought that biochemical alterations of the nerve root may not only lead directly to symptoms but may also increase susceptibility to injury from static or dynamic forces.

Cervical Radiculopathy Clinical Presentation

Patients with cervical radiculopathy present with various neurologic sequelae, which may include pain, numbness, paresthesias (burning and/or tingling), weakness, or decreased upper extremity reflexes (Fig. 5.4a–c, Table 5.1). Radicular weakness typically follows a myotomal pattern, whereas sensory disturbance follows a distinct dermatome [37] (Table 5.2). A review of over 800 patients with cervical radiculopathy found arm pain in 99.4%, sensory deficits in 85.2%, scapular pain in 52.5%, anterior chest pain in 17.8%, headaches in 9.7%, anterior chest and arm pain in 5.9%, and left-sided chest pain and arm pain in 1.3% [20]. Another study found surgical pathology correlated with neurologic symptoms as follows: diminished reflexes (82%), motor weakness (77%), and diminished sensation (65%) [54].

C3 Nerve Root

Pure C3 radiculopathy is uncommon. The C3 nerve root exits the largest foramen at C2–C3 and is the smallest cervical nerve root [34]. There is no distinguishing motor function of the C3 nerve root, and symptoms of radicular pain may present as neck pain or occipital headaches.

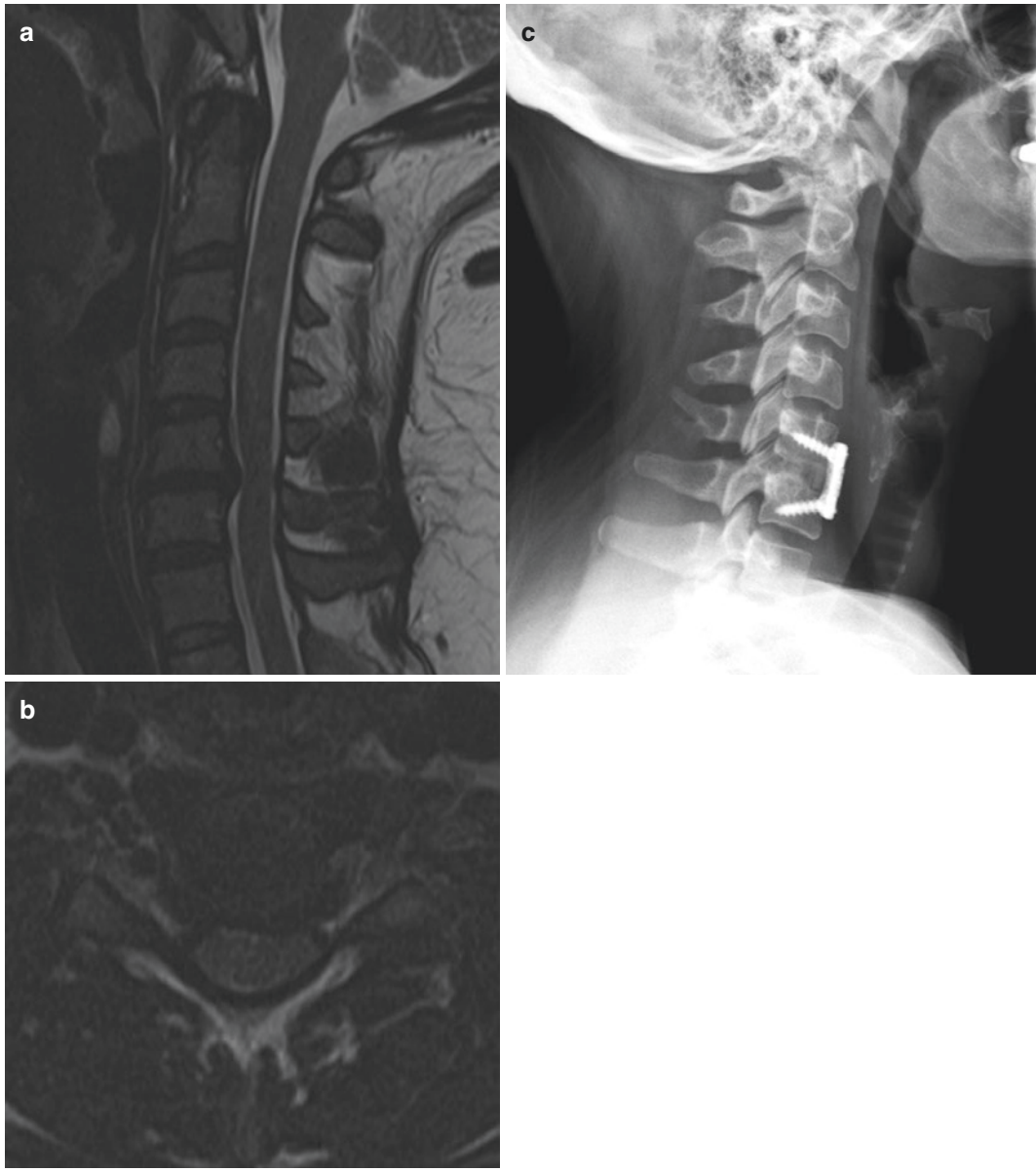

Fig. 5.4 (**a**-**c**) Case 1. A 37-year-old female presents with symptoms of mid-scapular pain and pain radiating down the left arm. On neurologic exam, the patient had subtle left wrist extension weakness and numbness to her left thumb. Reflexes were normal except for a slight diminished left brachioradialis reflex. Sagittal T2-weighted cervical MRI demonstrates a disc protrusion at the C5–C6 level (**a**). Axial T2-weighted cervical MRI at C5–C6 reveals left greater than right lateral recess and foraminal narrowing due to a broad-based disc protrusion. There is compression of the left C6 nerve root consistent with the patient's presenting radiculopathy (**b**). The patient eventually underwent surgical treatment with a C5–C6 anterior cervical discectomy and fusion (**c**)

Table 5.1 Cervical radiculopathy

Symptoms	Signs
Neck and/or radicular pain	Positive Spurling's test
Paresthesias	Hyporeflexia
Weakness	Shoulder abduction relief sign

C4 Nerve Root

Isolated C4 radiculopathy is also an uncommon presentation. C4 radiculopathy may present with pain radiating to the posterior neck, trapezius, and anterior chest.

Table 5.2 Cervical radiculopathy presentation

Disc Space	Nerve Root	Dermatome	Motor	Reflex
C1/C2	C2	Occiput		
C2/C3	C3	Upper 1/3 of neck	Diaphragm	
C3/C4	C4	Lower 2/3 of neck	Diaphragm	
C4/C5	C5	Lateral shoulder	Deltoid, biceps	Biceps
C5/C6	C6	Lateral forearm and thumb	Biceps, wrist extensors	Brachioradialis
C6/C7	C7	Posterior arm, digits 2 and 3	Triceps, wrist flexors	Triceps
C7/T1	C8	Ulnar palm, digits 4 and 5	Finger flexors	
T1/T2	T1	Medial arm	Interossei muscle	

C5 Nerve Root

C5 radiculopathy presents with pain and/or numbness over the lateral aspect of the shoulder and deltoid weakness. There may be minor weakness of the biceps, supraspinatus, and infraspinatus muscles. C5 radiculopathy may mimic shoulder pathology. Careful examination of the shoulder is crucial to make a correct diagnosis. The abductor relief sign, characterized by pain relief when placing one's hand over the head, is classic of cervical radiculopathy compared to pain with abduction seen with shoulder pathology. Of note, this sign is not limited to the C5 nerve root and may be seen with other lower cervical radiculopathies.

C6 Nerve Root

C6 radiculopathy is common and may lead to weakness of the biceps and particularly the extensor carpi radialis, which is only innervated by the C6 nerve root. C6 radicular weakness is characterized by impaired elbow flexion and wrist extension. Decreased biceps and/or brachioradialis reflexes may additionally be seen. C6 radicular sensation loss is over the thumb and lateral portion of the index finger. Radicular pain may start in the neck and radiate to the lateral arm and forearm into the thumb.

C7 Nerve Root

C7 radiculopathy is also a frequent presentation. The C7 nerve root innervates the triceps, and radiculopathy may lead to elbow extension or wrist flexion weakness and a diminished triceps reflex. Symptoms can include pain and sensory disturbance, including numbness and/or paresthesias radiating from the neck to the arm and digits 2–4. Horner's syndrome may also rarely be present [33].

C8 Nerve Root

The C8 nerve root innervates the hand intrinsic muscles and finger flexors. C8 radiculopathy may mimic ulnar neuropathy given their similar function. Weakness in the hand intrinsic muscles, wrist extensors, and wrist flexors may be present. Individuals may not be able to fully extend digits 4 and 5 (Benediction sign). Sensation over the medial forearm and digits 4 and 5 may be decreased, which can be distinguished from a pure ulnar neuropathy which results in splitting sensory loss of the ring finger. Pain typically radiates from the neck to the arm, medial forearm, and into digits 4 and 5. Horner's syndrome may also rarely be present in a C8 radiculopathy [33].

T1 Nerve Root

The T1 nerve root is a rare origin of radicular symptoms. Patients may present with hand intrinsic weakness without pain into the hand. Weakness of the first dorsal interosseous muscle (Froment's sign) may also be present. Similar to C7 or C8 radiculopathy, Horner's syndrome may also be a rare presentation [33].

Cervical Zygapophyseal and Discogenic Pain

It is important to note that cervical nerve roots are not the sole cause of neck, shoulder girdle, and upper extremity pain syndromes. Referred pain from small nociceptive neurons that innervate the zygapophyseal (facet) joints and disc space may mimic radicular pain symptoms [16, 43]. Unlike radicular symptoms, pain generated in the facet joints or disc space is not accompanied by sensory disturbance (i.e., numbness, paresthesias) or weakness. Radicular symptoms may be unilateral and/or bilateral, whereas pain associated with facet joints and/or the disc space is typically bilateral in nature. Table 5.2 summarizes the referred pain area from the facet joints and disc space [16, 43].

Cervical Myelopathy

Cervical myelopathy was first described in 1928 as neurologic signs or symptoms due to spinal cord dysfunction secondary to spinal canal narrowing or hypoperfusion of the spinal cord [34, 45] (Table 5.3). Cervical myelopathy is characterized by upper motor neuron and sensory impairment, often involving long ascending and descending spinal tracts. Cervical spondylosis and congenital spinal stenosis are the most common causes of cervical myelopathy [12], with cervical spondylotic myelopathy being the most common cause of spinal cord dysfunction in the elderly and the most common cause of nontraumatic spastic paresis. Other etiologies include ossification of the posterior longitudinal ligament, neoplasm, rheumatoid arthritis, infection, vascular disease, trauma, demyelinating disease, and metabolic disorders [55]. Cervical spondylotic myelopathy (CSM) is the most common worldwide cause of spinal cord dysfunction [27]. Early radiologic studies suggest 13% of men in the third decade and 100% of men over the age of 70, compared to 5% of women in the fourth decade and 96% of women over the age of 70, exhibit cervical degenerative changes that may lead to cervical myelopathy [23]. Multiple studies have assessed age as a risk factor for degenerative cervical myelopathy. Studies that have controlled for multiple cofounders show a positive association of age with myelopathy, whereas other conflicting studies fail to demonstrate correlation [10, 48, 58]. Gender has not been shown to be a risk factor for myelopathy [48, 58]. Radiologic studies and systematic reviews reveal that congenitally shortened canal and rheumatoid arthritis are factors associated with a high risk of developing cervical myelopathy [2, 30, 42].

Table 5.3 Cervical myelopathy

Symptoms	Signs
Paresthesias	Spastic gait
Gait disturbance	Positive Hoffman's reflex
Weakness	Positive Babinski's reflex
Problems with fine motor control	Hyperreflexia
Incontinence	Inverted radial reflex
Urinary retention	Weakness
Lhermitte's sign	Increased muscle tone

Cervical Myelopathy Pathophysiology

The pathophysiology of cervical spondylotic myelopathy is characterized by chronic progressive degenerative arthropathy. As described previously, age-related changes in the viscoelastic properties of the intervertebral disc lead to alterations in its biomechanical load-bearing capabilities. Ensuing redistribution of stress and strain across the cervical motion segment results in several pathologic changes. Initially, disc protrusion coincides with degenerative loss of disc height. Reactive endplate changes eventually progress to bridging osteophytic spur formation, in an attempt to minimize motion. The disc-osteophyte complex causes canal stenosis which may lead to cord compression and myelopathy (Fig. 5.5). Hypertrophy of the ligamentum flavum (Fig. 5.6) and progressive facet joint arthropathy develop to further off-load the

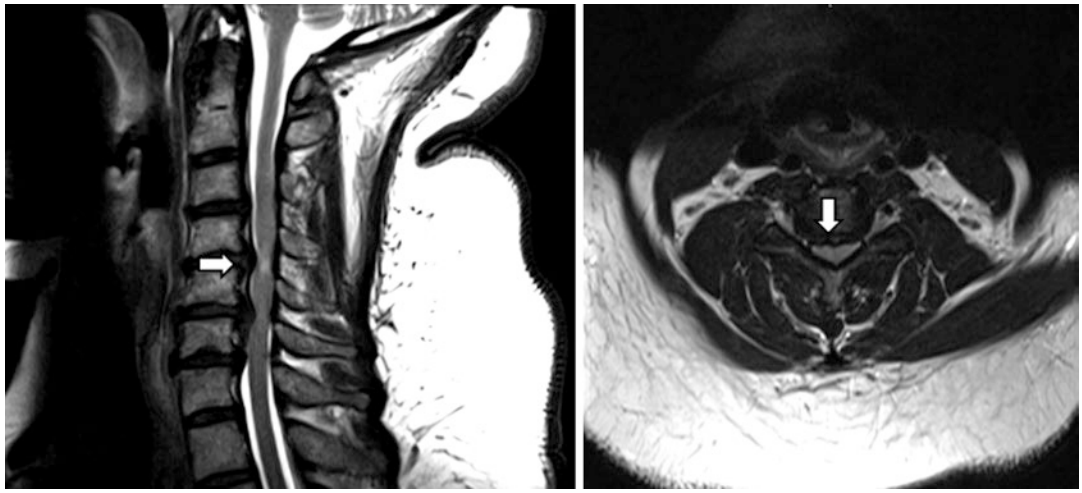

Fig. 5.5 MRI demonstrating multilevel disc-osteophyte complexes (*arrow*) causing canal stenosis and spinal cord compression. T2 signal change within the spinal cord suggests pathologic changes that correlate with myelopathy

degenerated disc. The combination of these factors (disc protrusion, osteophyte formation, ligamentum flavum hypertrophy, facet arthropathy) ultimately leads to narrowing of the spinal canal with potential compromise of the spinal cord. Congenital spinal stenosis and ossification of the posterior longitudinal ligament (Fig. 5.7) or ligamentum flavum are additional factors that may pathologically contribute to the development of cervical myelopathy.

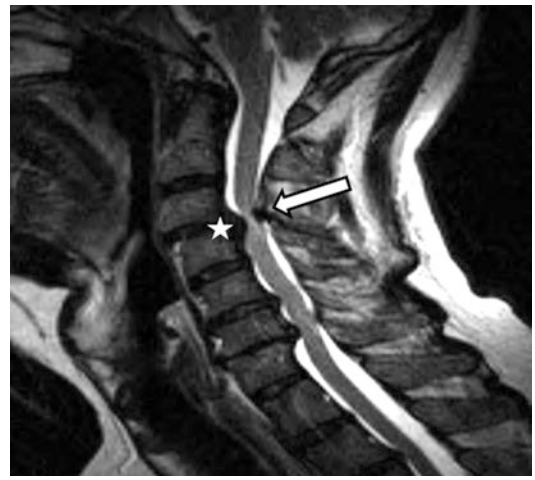

Fig. 5.6 MRI demonstrating ligament flavum hypertrophy (*arrow*) causing canal stenosis and spinal cord compression. A disc-osteophyte complex (star) with chronic degenerative anterolisthesis at the same level causing further stenosis and cord compression

Static Mechanical Compression-Induced Myelopathy

Static mechanical compression of the spinal cord leads to a cascade of pathophysiologic changes within the spinal cord ultimately resulting in spinal cord dysfunction and myelopathy. As discussed, common underlying etiologies of mechanical compression include spondylotic spinal stenosis, ossification of the posterior longitudinal ligament or ligamentum flavum, congenital stenosis, rheumatologic spinal disorders, and other acquired compressive pathologies (e.g., neoplasm or infection) [3]. Spinal cord histology in cervical myelopathy is characterized by cystic cavitation, gliosis, Wallerian degeneration of descending and ascending tracts, and loss of anterior horn cells [7, 47]. It deserves mention that mechanical compression injury from cervical spondylosis is distinct from that due to acute trauma. Unlike acute traumatic compression injury, in cervical spondylosis, there is no sudden mechanical insult, and consequently there is a noted absence of hemorrhagic necrosis within the spinal cord [27]. Further, the slow gradual

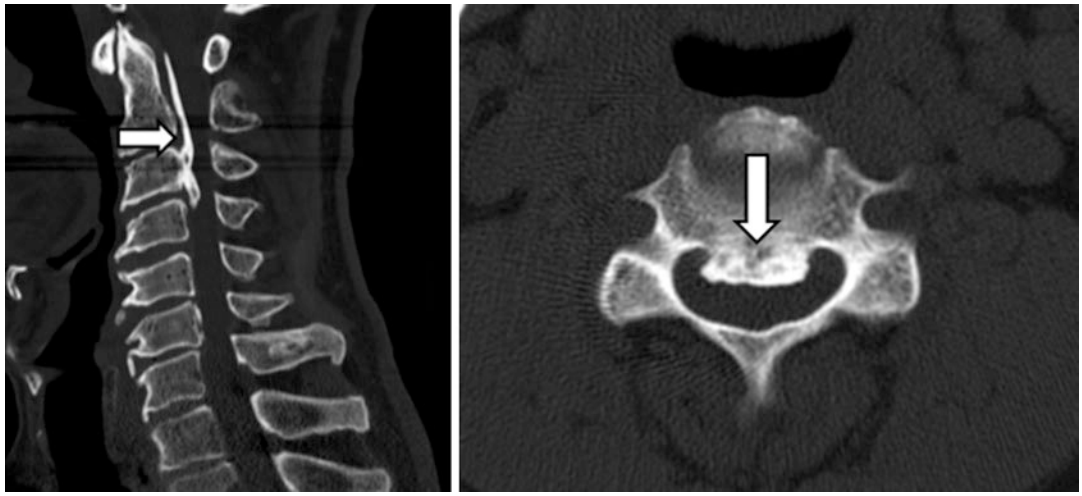

Fig. 5.7 CT demonstrating ossification of the posterior longitudinal ligament (*arrow*) causing canal stenosis and cord compression

development of spondylotic compression likely allows for coinciding compensatory neurologic and functional mechanisms to occur. This likely explains the chronic insidious symptoms, and often relatively minimal deficits in those with even severe radiologic spondylotic spinal cord compression, which is opposed to the immediate neurologic compromise seen in acute traumatic spinal cord injury (SCI) [27].

Static mechanical compression from cervical spondylosis is believed to cause myelopathy by direct injury to neurons via ischemic and apoptotic mechanisms. Gooding et al. first proposed the association of ischemic injury and myelopathy in a canine model of spinal cord compression [18]. They found hyalinization and hypertrophy in the walls of the anterior spinal artery after mechanical cord compression. Anterior and posterior compression of the spinal cord results in hypoperfusion through transverse arterioles originating from the anterior sulcal arteries and intramedullary branches to the central gray matter [15]. Foraminal stenosis compromises blood flow through the radiculo-medullary arteries leading to further decreased spinal cord perfusion [49]. Histologic evaluation of myelopathic spinal cords is characterized by areas of ischemic necrosis [14]. Corticospinal tracts are most affected by hypoperfusion and spinal cord ischemia [18], with the lower cervical spine being the most vulnerable to decreased perfusion [4]. Compression of spinal cord vasculature and hypoxia-induced cell injury of endothelial cells may additionally cause breakdown of the blood-spinal cord barrier (BSCB) leading to pathologic vasogenic edema [25]. A further distinction between pathologic changes in acute traumatic and spondylotic compression injury is that in traumatic SCI, there is repair to the BSCB, whereas in cervical spondylotic myelopathy, there is chronic disruption [29, 31]. While many studies suggest that alterations in spinal cord hemodynamics may play a role in myelopathy, other clinical and preclinical studies have countered with contradictory evidence of no or minimal spinal cord ischemia in the setting of myelopathy [1, 17, 21].

Apoptosis (programmed cell death) is the culmination of multiple biochemical processes resulting from primary and secondary injury to the spinal cord. In vivo models of cervical spondylotic myelopathy show that chronic extrinsic spinal cord compression results in Fas-mediated apoptosis of neurons and oligodendrocytes through action of caspase-8, caspase-9, and caspase-3 [56]. Animal models of spinal cord injury reveal apoptotic oligodendrocytes at the site of injury but more importantly distant demyelination of white matter tracts remote from the

primary injury epicenter [13, 28]. Histologic analysis of human spinal cord injury demonstrates oligodendrocyte apoptosis occurs prior to axonal degeneration [6]. This demyelination process within the spinal cord secondary to compression may explain the long tract findings at clinical presentation in patients with cervical myelopathy.

Dynamic Compression-Induced Myelopathy

In addition to static compression, studies indicate that dynamic compression of the spinal cord may have a significant role in myelopathy development. Cadaveric research has shown alterations in the anteroposterior spinal canal diameter in response to tension-compression forces and flexion-extension changes [11]. From tension to compression, the canal diameter decreases 10.1% secondary to changes related to the disc and decreases 6.5% from the ligamentum flavum [11]. From flexion to extension, the canal diameter decreases 10.8% secondary to changes related to the disc and decreases 24.3% from the ligamentum flavum [11]. More recent clinical studies using dynamic magnetic resonance imaging demonstrate flexion-extension-induced spinal canal narrowing due to ligamentum flavum buckling and shingling of the lamina in hyperextension [9]. Narrowing of the spinal canal <11 mm during flexion-extension is correlated with cervical myelopathy [35]. Lhermitte's sign, electrical shock-like sensation, or pain radiating down the back with neck range of motion is a classic clinical manifestation of cervical extension-induced dorsal column compression.

Stretch and Shear Force-Induced Myelopathy

Dynamic movement of the cervical spine not only results in spinal canal narrowing but may further cause stretch and shear forces leading to axial strain-induced cord injury [19]. Yuan et al. showed an elongation of the spinal cord up to 10% of its length on the posterior surface and 6% on the anterior surface with full flexion from the neutral position [57]. Human cadaveric models show that the spinal cord is initially compliant to stretch but loses this compliance as axonal fibers straighten out and bear tensile load [5]. Histologic studies demonstrate that stretch and shear injury variably affects spinal cord gray and white matter, with gray matter being more rigid and thereby more susceptible to increased stretch of the spinal cord [22]. Stretch and shear injury leading to axonal dysfunction has been confirmed with in vitro electrophysiologic studies revealing stretch-induced disruption of compound action potentials [41].

Cervical Myelopathy Clinical Presentation

Patients with myelopathy may present with a variety of neurologic signs or symptoms that are often progressive in nature (Fig. 5.8a–c). Symptoms may include loss of fine motor coordination in the hands, numbness or paresthesias in upper or lower extremities, sensation of heaviness or weakness in the legs, gait imbalance, hyperreflexia, Lhermitte's sign, and, in late stages, bowel or bladder dysfunction [12]. Loss of fine motor control in the hands may present as dropping objects, difficulty writing, or trouble buttoning a shirt. Cervical myelopathy leads to characteristic signs noted on physical exam. Spastic gait and/or increased upper extremity tone are late-stage signs in cervical myelopathy secondary to loss of normal upper motor neuron tonic inhibition. Hoffman's and Babinski's signs are two common pathologic reflexes that may be seen in cervical myelopathy. Hoffman's sign is characterized by flexion and adduction of the thumb and concurrent flexion of the index finger with stimulation of the extensor tendon of the third digit. Babinski's sign (plantar reflex) is concurrent extension of the great toe with stimulation of the lateral aspect of the plantar surface of the foot. Another pathologic reflex

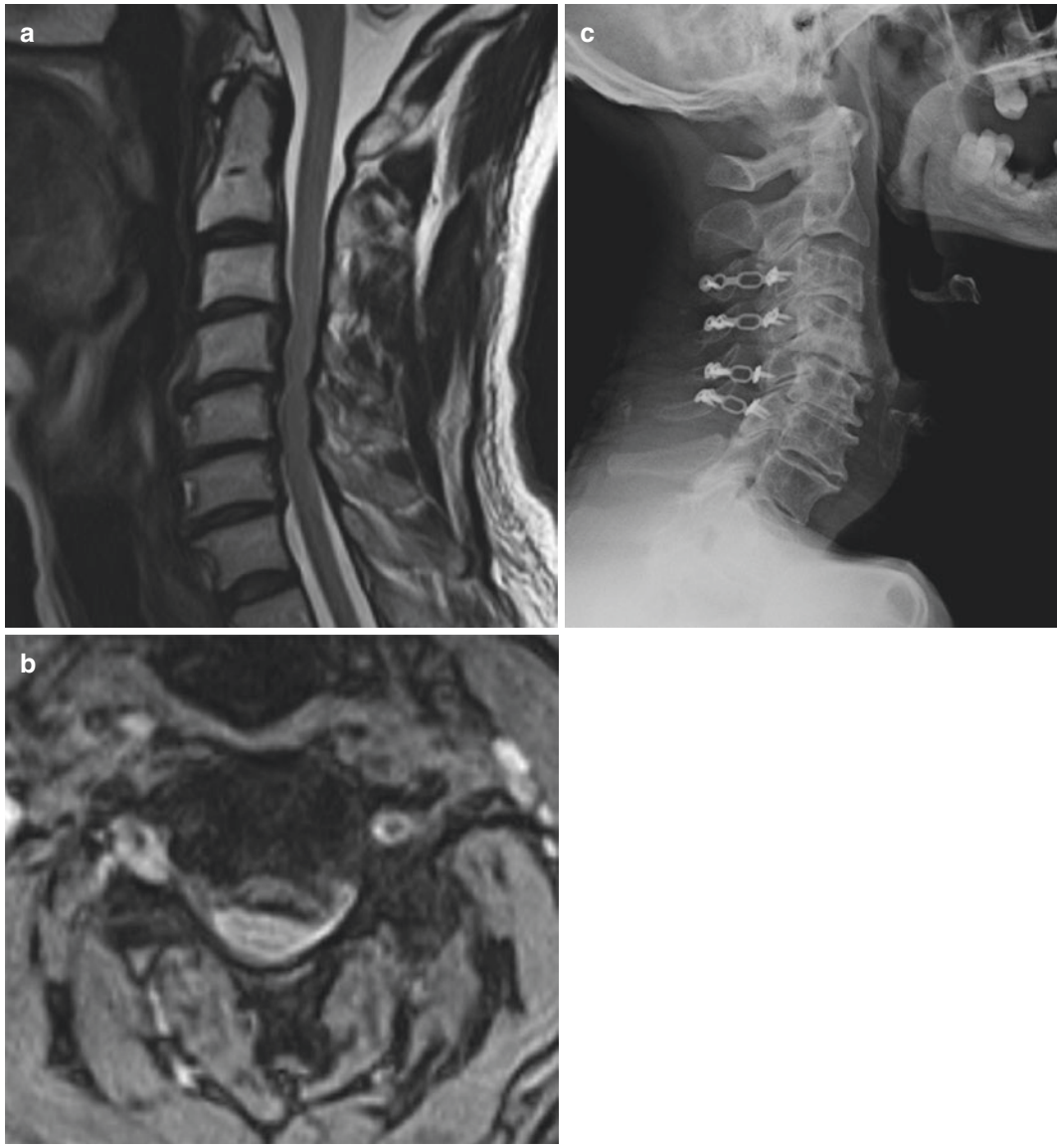

Fig. 5.8 (**a**–**c**) Case 2. A 55-year-old male presents with symptoms of progressive loss of hand coordination and gait instability. Neurologic examination was notable for impaired tandem gait, brisk patellar tendon reflexes, and positive Hoffman's sign. Sagittal T2-weighted cervical MRI demonstrates cervical spondylosis with spinal canal stenosis and cord compression from C3 to C6 (**a**). Axial T2-weighted cervical MRI demonstrates ventral spinal canal narrowing secondary to broad-based disc osteophyte formation with T2 signal abnormality within the spinal cord (**b**). The patient underwent surgical treatment via laminoplasty for posterior decompression (**c**)

that may be seen in cervical myelopathy is the inverted radial reflex; tapping the brachioradialis tendon causes wrist and finger flexion. Unlike cervical radiculopathy, significant neck or extremity pain is often notably absent in cervical myelopathy [12].

Conclusion

The pathobiology of cervical radiculopathy and myelopathy involves a combination of static and dynamic mechanical compressive factors, as well as biochemical processes that ultimately

lead to nerve or spinal cord injury. In cervical radiculopathy, the pathophysiologic mechanisms result in motor and sensory loss in the distribution of select spinal nerve roots with clinical symptomatology along a myotome or dermatome. Cervical myelopathy is a more significant pathophysiologic process, which ultimately leads to disruption of long ascending and descending spinal cord pathways. As a result, the clinical manifestation of myelopathy is characterized by loss of combined motor and sensory function involving multiple spinal levels with the hallmark of upper motor neuron dysfunction. Improved understanding of the underlying pathobiology of radiculopathy and myelopathy may ultimately lead to improved management strategies.

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