20 Pathophysiology of Cervical Myelopathy: Biomechanics and Deformative Stress

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SUMMARY OF KEY POINTS

- Clinical and neurobiologic studies support mechanical deformity of the spinal cord as an important cause of myelopathy.
- Static and dynamic elongation and displacement of the spinal cord, such as occurs in cervical kyphosis, may result in physiologic tethering of the spinal cord, and consequent myelopathy.
- Dynamic imaging is important to determine whether there is transient compression, deformity, or stretching of the spinal cord.
- High-tensile loading leads to immediate changes in axolemmal permeability and rapid disruption of axoplasmic flow.
- Axon retraction bulbs result from stretch injuries of the spinal cord within days, and they may progress to axonotmesis.
- Stretching neurons deforms Na channels, allowing increased Na, loss of the electrochemical gradient, and pathologic calcium influx.
- Deformation of neurons is an epigenetic stimulus-altering gene expression.

Cervical spondylotic myelopathy (CSM) is a well-described clinical syndrome that evolves from a combination of etiologic mechanisms. The strong association between a narrowed, spondylotic cervical spinal canal and the development of CSM has led to the formulation of a relatively simple pathoanatomic concept: a narrowed spinal canal causes compression of the enclosed cord, leading to local tissue ischemia, injury, and neurologic impairment. However, this simple mechanism fails to explain the spectrum of clinical findings observed in CSM, particularly the development of significant neurologic signs in patients without evidence of static cord compression.

Current support for a biomechanical etiology of CSM comes from three areas: clinical studies of cervical mobility in patients with CSM, histopathologic studies of spinal cord tissue from patients with CSM, and biomechanical studies that have led to an improved understanding of the material properties and biomechanical behavior of spinal cord tissue under various physiologic and pathologic conditions. A growing body of evidence indicates that spondylotic narrowing of the spinal canal results in increased strain and shear forces, and that these pathologic deformative forces cause both diffuse and focal axonal injuries in the spinal cord. A greater appreciation for the biomechanical causes of spinal cord injury more fully recognizes the clinical and pathologic findings in various studies of spinal cord injury and better explains the occurrence of clinical myelopathy in patients without static cord compression.

PATTERNS OF CERVICAL SPONDYLOTIC MYELOPATHY

Clinical myelopathy typically appears in late adulthood in the setting of progressive degenerative changes, including cervical disc degeneration, osteophytic spur and transverse bar formation, posterior longitudinal ligament calcification, ligamentum flavum thickening, and osteoarthritic facet hypertrophy.[1-3] Retrospective observational studies indicate that development of CSM is more common in patients with underlying congenital stenosis of the spinal canal. A sagittal spinal canal diameter of less than 12 mm is strongly associated with signs and symptoms of myelopathy, whereas a diameter greater than 16 mm confers a low risk.[4-8] The wide variation in radiologic technique may, however, result in various degrees of magnification error, prompting the use of the ratio of Pavlov (anteroposterior [AP] diameter of the spinal canal divided by the AP thickness of the vertebral body); normally, the ratio should be greater than 0.8.

Progressive encroachment on the spinal canal by ventral and dorsal anatomic structures may result in a compression that occurs only transiently during physiologic cervical range of motion. The appearance of clinical signs and symptoms arising from this condition has been described as "dynamic stenosis." With progressive narrowing of the spinal canal, dynamic compression may eventually evolve into static compression of the enclosed spinal cord and the appearance of classic CSM. Dynamic compression of the spinal cord may therefore occur within the normal physiologic range of motion with pathologic changes of the spine, or it may result from pathologic range of motion in a spine where there is no spondylotic change. That is, the injury to the spinal cord can result from pathologic motion causing a "pincer phenomenon."[9,10] A pincer phenomenon occurs where unstable segments sublux, on flexion or extension, and cause a dynamic spinal cord compression. Most often the cord is compressed, as a result of retrolisthesis between the lower, posterior vertebral edge and the upper edge of the lamina of the next vertebral level, or as a result of bulging of the disc upon flexion or extension.[11] Pathologic movement due to segmental instability may also result in pathologic stretching of the spinal cord upon flexion or extension, without demonstrable compression of the cord.[11-15]

In extension of the cervical spine, the tracts in the dorsal half of the spinal cord undergo five times the compression of the tracts in the ventral half of the spinal cord. In flexion, the tracts in the dorsal half of the cord stretch far more than those ventrally located.[10,14,16] Furthermore, in the presence of a kyphosis, the cervical cord is anatomically displaced posteriorly, suffering significant elongation and distortion in the process. Where there is a focal kyphosis due to segmental instability, there is significant distortion of the spinal cord: in essence the spinal cord becomes physiologically

tethered over the focal kyphosis in what is termed the *sagittal bowstring effect.*[11,17]

The importance of dynamic flexion extension imaging should be apparent; a cervical spine may have a normal appearance in a neutral view while manifesting significant kyphosis on the flexion view.[18] This is an important concept in the increasingly recognized population of patients with hypermobility connective tissue disorders, including Down, Marfan, and Ehlers-Danlos syndromes, which can exhibit ligamentous instability and manifest a proclivity toward pathologic motion from cervical—especially atlantoaxial and craniocervical—segmental instability.[19-21]

HISTOPATHOLOGY OF CERVICAL SPONDYLOTIC MYELOPATHY

The theory that ischemic injury is the pathophysiologic basis of CSM originates in early histologic studies of cervical myelopathy that revealed several changes consistent with ischemic tissue damage. These include cystic cavitation, gliosis, anterior horn cell dropout, and prominent involvement of the central gray matter, as well as Wallerian degeneration of the posterior columns and corticospinal tracts.[2,22-24] In these studies, the most severe histologic changes were observed at the level of ventral spondylotic bars, with the most visible histologic changes occurring in the lateral funiculi of the spinal cord, particularly the corticospinal tracts. The anterior columns and dorsal region of the dorsal columns appeared to demonstrate the least extent of injury-related change.

Attempts have been made to correlate the severity of histopathologic findings with the range of clinical findings in patients with CSM. In general, less severe myelopathy has been associated with changes confined largely to the lateral funiculi, whereas more severe cases appear to be associated with involvement of the medial gray area and ventral aspect of the dorsal columns, as well as gliosis and anterior horn cell dropout. In cases of severe CSM there is extensive Wallerian degeneration, proceeding proximally and distally from the site of spinal cord compression.

SPINAL CORD ISCHEMIA AND CERVICAL SPONDYLOTIC MYELOPATHY

The anatomic basis for the ischemic insult proposed in CSM has been attributed to various mechanisms, including compression of radicular feeders in the neuroforamina, compromise of venous drainage by ventral spondylotic bars, and compression of the anterior spinal artery, as well as its ventral branches.[25,26] Several animal studies support the concept of a potential role for compressive ischemia in the pathogenesis of CSM.[27-29] Cadaver studies have demonstrated that flattening of the cervical spinal cord is associated with elongation of the laterally directed terminal branches of the central arteries arising from the anterior spinal artery, as well as elongation of the penetrating branches of the lateral pial plexus (corona radiata). It is hypothesized that attenuation of these transversely directed arteries results in decreased arterial blood flow to the corticospinal tracts. Shortening of the ventral-dorsal dimension of the spinal cord, however, results in widening of the arteries directed in the ventral-dorsal direction and relative preservation of blood flow to the anterior columns. These findings might explain the relative vulnerability to injury of the laterally positioned corticospinal tracts, compared with the anterior columns.[30]

Clinical studies strongly suggest that compression and ischemia alone do not fully explain the pathogenesis of CSM. Despite observational studies associating CSM with various anatomic factors, such as the presence of decreased ventral-dorsal spinal canal diameter, subluxation, and dorsal osteophytes, at least one study has demonstrated that these factors hold no significant predictive value in terms of identifying which patients are at risk for clinical progression of their myelopathy.[31] Several other studies have also failed to identify an association between the degree of spinal stenosis and spinal cord compression and clinical prognosis.[7,26,32] Moreover, surgical decompression that results in expansion of the spinal canal and relief of compressive pressures does not consistently alter the natural history of CSM.[33] Ebersold and colleagues performed a retrospective review of 100 patients with CSM undergoing surgical decompression, with an average 7-year follow-up, and concluded that decompression alone resulted in no clear, long-term improvement. Two thirds of patients experienced initial clinical improvement, but half of these demonstrated subsequent clinical deterioration. At final follow-up, only a third of the original group were improved, leading the authors to conclude that long-term outcome was not predicated on the presence or severity of spinal cord compression and ischemia, but on other, "nonvascular" factors.[34]

BIOMECHANICAL FACTORS AND CERVICAL SPONDYLOTIC MYELOPATHY

There is a growing body of evidence indicating that abnormal or excessive motion of the cervical spine is strongly associated with clinical progression of CSM. In a retrospective clinical review, Adams and Logue[26] demonstrated a cervical flexion-extension arc in excess of 40 degrees was the most significant variable in predicting poor clinical outcome in patients with CSM.[26] Similar retrospective studies have been performed by Barnes and Saunders,[31] as well as by Yonenobu and coworkers,[32] in which patients with a flexion-extension arc of greater than 60 degrees after laminectomy were at increased risk for development of progressive myelopathy. In contrast to the relatively poor results after simple decompression for CSM, several studies demonstrate excellent clinical results associated with the elimination of abnormal cervical motion. Using a simple neck brace to restrict cervical motion often leads to improvement in patients with cervical myelopathy from disc protrusions.[35] The largest series of patients undergoing ventral decompression and fusion for CSM demonstrated an 86% improvement rate, with no significant deterioration.[36] Uchida and colleagues[17] discovered that among patients with CSM who had kyphotic deformity in excess of 10 degrees, correction of sagittal alignment of the vertebrae significantly improved neurologic outcomes. Uchida and colleagues stated that a "kyphotic alignment may contribute to cervical myelopathy," that longitudinal distraction is a factor in progressive spinal cord dysfunction, and that the pathophysiologic mechanism is similar to that of tethered cord syndrome.[17] Overall, surgical fusion through a variety of approaches has been associated with favorable clinical results, including ventral decompression and fusion without instrumentation[34] or with ventral plating,[37-41] and dorsal decompression with instrumented fusion.[42-45]

The significant clinical recovery experienced by most myelopathic patients after decompression and fusion indicates that neurologic deficits resulting from cervical myelopathy are recoverable.[36,38-40,44,45] Moreover, the rapid improvement experienced by many patients after surgery suggests that these patients do not have irreversible, ischemic histologic changes demonstrated in many early pathologic studies. In contrast, failure of some patients to improve clinically after decompression and fusion may be a result of irreversible spinal cord injury. Histologic examination of spinal cord tissue from these patients may reveal severe ischemic injury.[2]

PATHOPHYSIOLOGY OF DEFORMATIVE STRESS INJURY OF THE CERVICAL SPINAL CORD

The significance of spinal stenosis and spinal cord compression in early CSM may not be the generation of local ischemia but rather the creation of a tethering effect, which results in production of local, potentially injurious, tissue strain, and shear forces. The concept that increased cervical mobility, coupled with kyphotic deformity, results in spinal cord elongation and increased axial strain forces is well documented.[13,15,17,25,26,30,31,46-51] Several studies have demonstrated the adverse effects of even low-grade mechanical stretching on neural tissues. During normal motion, large axial strains occur in the cervical spinal cord.[52] The white matter of the spinal cord can be viewed as an axial array of parallel fibers, with individual fibers demonstrating variable levels of crimping. As a whole the cord is initially compliant to stretch, but it becomes progressively stiffer as the fibers straighten and begin to bear tensile load.[50] Rapid occurrence of these strains can exceed the material properties of the tissue, leading to tissue disruption and transient or permanent neurologic injury. The degree of injury appears to be related to the peak strain of the tissue and the loading rate.[53]

Cadaver studies suggest that even physiologic flexion of the cervical spine leads to stretching and to the production of strain forces in the neuraxis.[30] Flexion of the spinal column has been found to result in significant elongation of the spinal canal, with concomitant stretching of the spinal cord. During physiologic flexion of the head and trunk in rhesus monkeys, net movement of the spinal cord occurs from the upper spine downward to the level of C4-5, whereas net movement of the spinal cord occurs upward below this level.[46] Net movement occurs to a greater extent below C4-5, with 1.6 mm of movement at C1 and 6 mm of movement at T3. The amount of spinal cord stretch occurring at each level is proportional to the degree of flexion at the adjacent intervertebral disc space. Thus, forces that are generated in the spinal cord upon flexion can be visualized with neutral and flexion magnetic resonance images (MRIs) of the cervical spine. Flexion of the neck results in significant elongation of the enclosed spinal cord (Fig. 20-1). The increase in length (l) over the original length of the same section of the spinal cord (lo) provides the strain (ε), thus:

$$E = 1/1.$$

At the lower cervical spine, where the amount of flexion tends to be greatest, local spinal cord strain can be excessive.[12] Where there is excessive flexion, the strain produced at the cervicothoracic junction can reach 0.2 (i.e., 20% stretch), the strain level at which the giant squid axon ceases to function.[53] This phenomenon might explain the clinical observation that signs are often localized to levels apparently remote from the level of stenosis (e.g., hand intrinsic muscle wasting with high cervical stenosis).

In the absence of a compressive pathologic process, the natural elongation of the spinal cord that occurs with neck flexion and hyperextension is distributed over the entire length of the spinal cord. However, with tethering of the spinal cord, as a result of local compression, the axial strain cannot be distributed throughout the cord and is instead limited to the segment of cord between the distracting force and the tethering point. Local spinal cord degenerative changes are frequently identified adjacent to thickened dentate ligaments, which suggests that localization of injurious mechanical forces at these levels may be associated with the tethering effect of the ligaments.[51,54] A biomechanical study of the material properties of the dura mater indicates that elastic behavior is uniform throughout the length of the spinal canal; however,

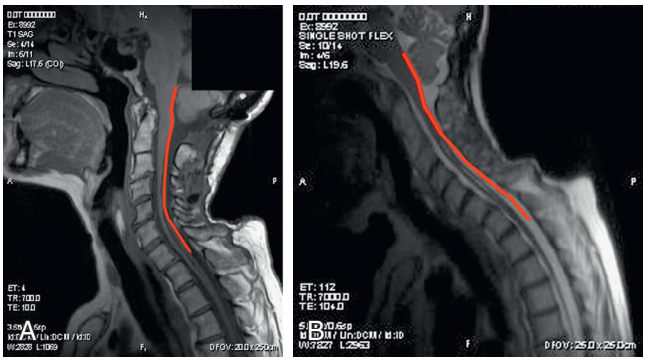

Figure 20-1. Strain within the cord on regular flexion. **A,** The red line represents a hypothetical white matter tract measured from the base of the C7 level to the pontomedullary line. **B,** The same tract is shown in flexion. The indicated portion of the tract increases in length from 94 mm to 116 mm, representing a strain ε of approximately 0.24.

strain forces are significantly greater in the cervical region than in either the thoracic or lumbar region.[55]

The tethering action of the dentate ligaments may be responsible for accentuating the effect of tensile spinal cord stress and exacerbating local tissue injury. Moreover, it has been suggested that dorsal displacement of the spinal cord, as a result of the presence of ventral spondylotic bars, may lead to stretching of the dentate ligaments and tethering of the cervical cord through the ventrolaterally positioned nerve root sleeves. Repetitive and persistent microtrauma to these nerve root sleeves may lead to the progressive thickening that has been observed with age.[54] Therefore, axial tension generated in the spinal cord during physiologic motion may be amplified at certain levels, as a result of two separate factors—overall spinal canal lengthening and the local tethering effects of the dentate ligaments.

Several investigators have attributed delayed, progressive cervical myelopathy to a combination of underlying structural kyphosis and abnormal or excessive cervical motion.[11,17,25,26,47] Dynamic lengthening of the cervical spinal cord that occurs during neck flexion is magnified in patients with cervical kyphosis. Conversely, kinematic MRI studies have demonstrated that lengthening of the spinal cord also occurs during neck extension in some patients with fixed kyphotic deformity of the cervical spine. In the setting of static spinal cord compression and superimposed instability, cervical extension can also lead to aggravation of the cord impingement and significant upper cervical spinal cord elongation.[56]

MATHEMATICAL MODELS OF SPINAL CORD STRETCH INJURY

Numerous mathematical models for spinal cord stretch injury have been developed. Levine[51] represented the spinal cord as a simplified solid material with uniform elastic properties to predict the three-dimensional stresses experienced during physiologic motion and in spondylosis. According to this model, flattening of the cord is not a result of ventral-dorsal compression, but rather the consequence of laterally directed tension arising from the dentate ligaments, which tighten in flexion. This model, with a ventral spondylotic bar and tethering dentate ligaments, predicts maximal stresses in the lateral funiculi. The model provides a possible explanation for the characteristic histologic findings in CSM, in which there is relative sparing of the anterior and posterior funiculi. It also explains why histopathologic changes are found over a relatively extended segment of spinal cord tissue, as opposed to

being limited to the point of compression. However, the importance of the dentate ligaments in the etiology of CSM is brought into question by the inconsistent results of sectioning these ligaments at the time of surgery.[57]

Breig[47] also developed a mechanical model to explain some of the apparent inconsistencies found in histologic studies of CSM. For instance, in addressing the question of why some chronic, ventral compression injuries result in predominantly dorsal cord injury, cadaver models demonstrated that a compression force applied ventrally to the spinal cord in the presence of stenosis creates a pincer mechanism, resulting in increased axial tension in the cord and fissuring opposite the side of compression. In this model the spinal cord is represented as a viscoelastic cylinder that, when compressed from the sides, exhibits net tissue creep to the free ends of the cylinder. As a result, tension forces are created perpendicular to the plane of compression. With mild compressive deformation of the spinal cord, elastic stretch of the axis cylinders occurs. However, when the ventral-dorsal diameter of the spinal cord is reduced by 20% to 30%, axial tension forces exceed the material properties of the tissue and result in tearing of axial fibers. The stress field produced by this pincer mechanism is multidirectional, and secondary shearing forces are also created. This model offers an explanation to the histopathologic findings of others, in which ventral compression of the upper spinal cord resulted in stretch and shear injury to myelin and neural elements.[48]

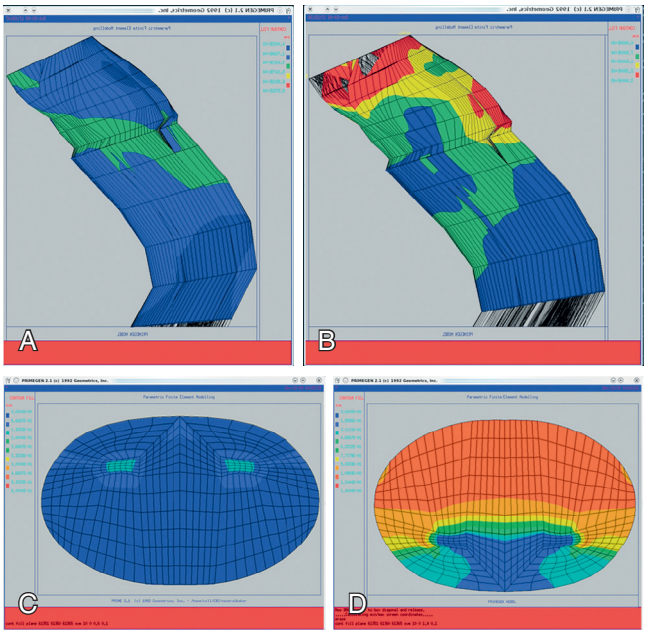

Figure 20-2. Finite element analysis of a portion of the cervical spine of the patient whose MRIs are shown in Figure 10-1. **A,** Sagittal view demonstrating the stresses on flexion. **B,** Sagittal view demonstrating more severe stresses on addition of local compression due to retroflexed odontoid with same degree of flexion as in **A**. **C,** Axial view at C1 of **A**. **D,** Axial view at C1 of **B**.

FINITE ELEMENT MODELS OF SPINAL CORD STRETCH INJURY

Researchers have produced mathematical models of the cord using finite element analysis, a method adapted from materials science and fluid mechanics. Finite element analysis reduces a continuous structure into discrete, finite "brick" elements. This allows the approximation of partial differential equations by a linear system of ordinary differential equations, which can then be solved by numerical methods with the appropriate boundary conditions.[58] In this particular case, the equations concern mechanical strain (stretch), "out of plane" loading (shear due to transverse compression, such as from a retroflexed odontoid process), and material properties such as the Young modulus of elasticity or the Poisson ratio. Ichihara and colleagues[13] used finite element analysis to simulate the cervical spinal cord under compression and showed that different amounts of stress at a given strain rate were to be expected owing to the differing material properties of gray and white matter. Kato and coworkers[15] showed that the addition of a small amount of flexion to a model with static compression significantly increased predicted stresses, with the majority of stresses in the anterior and posterior horns. Others correlated increased deformative stresses in the corticospinal tracts, as predicted by the finite element analysis, with neurologic deficits in subjects with cervical and medullary symptoms.[59] Elevated stress levels due to strain occurred during normal neck flexion in the spinal cord at the C1 level of one patient (MRIs from this patient are shown in Fig. 20-1); the addition of compression (shear) from a retroflexed odontoid process generates much higher stress levels with the same degree of flexion (Fig. 20-2).

SPINAL CORD TETHERING AND SHEAR INJURY

Studies involving the tethered spinal cord syndrome may also contribute to a better understanding of the pathogenesis of CSM. Stretch injury is now widely accepted as the principal cause of myelopathy in tethered cord syndrome. The symptoms and clinical findings of pain, numbness, weakness, pes cavus, scoliosis, and bowel and bladder dysfunction have all been attributed to stretching injury of the spinal cord.[16,60-65] The degree or amount of traction on the conus medullaris determines the age of onset of symptoms. Extensive tethering and severe stretching of the conus medullaris results in neurologic disturbances in infancy, whereas a lesser degree of tethering often remains subclinical until adulthood, when symptoms may become manifest in the setting of an acute event (i.e., hyperflexion injury) or chronic process (e.g., development of ventral disc or bone protrusions).[66] Although clinical manifestations of tethered cord syndrome are more commonly referable to the lumbosacral spinal cord, many neurologic findings are referable to the cervical cord. For example, long tract involvement in tethered cord syndrome may lead to hand numbness and poor coordination, as well as upper extremity hyperreflexia and even speech difficulties. Quadriparesis has also been reported.[67] The phenomenon of increased strain supports the hypothesis that tension in the spinal cord might be transmitted to the brain stem and remote segments of the cord. Injury to the large-diameter fibers of the corticospinal tracts may occur some distance from actual tethering and result in mixed upper and lower motor neuron deficits.[66]

Experimental studies involving the lumbar and sacral spinal cord of cats have demonstrated that acute tethering is very traumatic to spinal cord tissue, particularly when stretching occurs repeatedly.[68] Spinal cord elongation is most pronounced immediately adjacent to the point of application of the tethering force. Under low levels of tension the spinal cord demonstrates purely elastic behavior and returns to normal resting length. At greater tension, plastic deformation occurs. Portions of the spinal cord near the point of application of stretch remain elongated by 7% over the original length, even after release of tension. Tissue dysfunction in tethered cord syndrome has been associated with impairment of oxidative metabolism. The relationship of tissue ischemia to spinal cord

stretching in this syndrome is unclear. Although a tethered cord may result in permanent neurologic deficit, the fact that surgical untethering usually results in significant improvement of sensorimotor and bladder function indicates a degree of reversibility that militates against a purely ischemic etiology.

A guinea pig model of spinal cord stretch injury has been developed in which the filum terminale was tethered and attached to a 5-g weight. Tethering resulted in significant delay and decreased amplitude of somatosensory evoked potentials. Lipid peroxidation and hypoxanthine levels were significantly increased. Electron microscopic examination of tissue revealed potentially reversible histologic changes, such as edema, destruction of the gray-white junction, axonal injury with loss of neurofilaments, and evidence of myelin sheath damage.[69] Demyelination of corticospinal tracts in trauma is similar to the demyelination and edema seen in the posterolateral funiculi of patients with CSM. Autopsy studies of patients with rheumatoid arthritis and myelopathy have revealed edema localized to the posterolateral funiculi, as well as axonal retraction balls, suggestive of stretch-related injury without evidence of significant ischemia.[48]

The finding that tethering of the spinal cord in one region leads to generation of stretch and shear forces remote from the site of tethering or compression is directly applicable to numerous pathologic processes throughout the spine. The spinal cord can be tethered at any level by scarring, external compression, or spinal deformity. Spinal cord deformation over a large disc herniation at the apex of a thoracic kyphosis can contribute to stretch and shear injury remote from the locus of deformation.[47] Similarly, deformation of the medulla spinal junction over the odontoid process in basilar invagination results in both local and remote neurologic dysfunction (e.g., diplopia, dysphagia, dysarthria, vertigo), as well as sensorimotor deficits.[70] Although these effects may also be explained by ischemic injury, local ischemia has not been found.[48] Again, correction of medulla spinal deformity through surgical removal of the odontoid process or traction/reduction and occipitocervical stabilization typically results in significant clinical recovery.[71-73] Disturbances of sleep and alterations in central respiratory function have been attributed to ventral deformity of the upper spinal cord and lower brain stem in basilar invagination, and these disturbances have been reversed by correction of the ventral cervicomedullary deformity.[49]

The neurologic dysfunction observed in association with an abnormally acute clivo-axial angle (CAA) is the result of deformation and deformative stress injury of the neuraxis. Kim and colleagues[74] determined that an abnormal CAA caused subtle deformity of the upper spinal cord and medulla, resulting in headache, weakness, and sensory changes, as well as brain stem–related symptoms. Kubota and associates[75] found that syringomyelia was more likely to resolve after treatment of a Chiari malformation if the CAA was more obtuse and the brain stem therefore straighter. Henderson and coworkers[59] found that normalizing the CAA (increasing the angle to the normal 160 degrees) significantly improved neurologic function in a cohort of children with cervicomedullary syndrome due to an abnormal CAA. There is thus growing evidence that an abnormally acute CAA is indicative of a specialized form of brain stem tethering, which may produce the pattern of elevated stresses observed throughout the cord in cervical flexion myelopathy and CSM (Fig. 20-3).

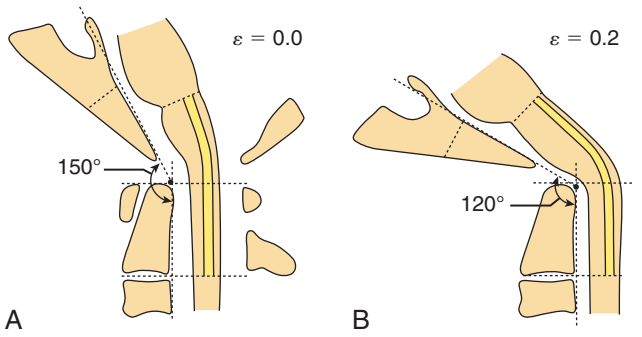

Figure 20-3. A, The brain stem and upper spinal cord in the normal individual, with a normal clivo-axial angle (CAA) greater than 150 degrees, shows no strain (ε = 0.0) in a nerve column *(shaded)* in the dorsal neuraxis. **B,** The brain stem and upper spinal cord in a patient with an abnormal acute CAA (in this case CAA = 120 degrees) results in lengthening of the brain stem and spinal cord. The nerve column in the posterior neuraxis becomes stretched (ε = 0.2), resulting in neurologic deficits.

HISTOPATHOLOGY OF SPINAL CORD SHEAR INJURY

If neuraxial deformation, abnormal motion, and stretch injury are the primary causes of CSM and similar neurologic syndromes, then the histopathologic manifestations appear to be myelin edema and reactive axonal changes. A form of spinal axonal injury has been observed that is similar to the diffuse axonal injury (DAI) seen in the brain after deceleration injuries.

DAI is the most common brain injury resulting from blunt head trauma, and patient morbidity has been directly associated with the extent of DAI.[26,76] Experimental primate models have demonstrated that the location and quantity of axonal changes directly correlate with observed morbidity.[77,78] Clinical and pathologic studies have revealed that axonal injury is a component of traumatic brain injury throughout the spectrum of severity, from concussion to severe forms of prolonged coma.[79] Despite these histopathologic observations, the pathogenesis of DAI remains unclear. An early hypothesis speculated that tearing of the axon at the time of injury resulted in expulsion of a ball of axoplasm into the brain parenchyma.[80,81] However, DAI studies have demonstrated that axons undergoing shear strain do not undergo immediate disruption, but rather a nondestructive injury manifests as axonal swelling in internodal regions.[82] Axonal stretch at the time of injury results in axolemmal damage, disruption of axon transport and metabolism, and the delayed formation of a retraction ball or reactive axonal swelling.[82,83] This focal swelling is thought to be a prestage secondary axotomy.[84-87] Studies have demonstrated that traumatic axonal injury results in impairment of anterograde axonal transport. In a guinea pig optic nerve model, 17% of axons demonstrated injury within 15 minutes of an applied stretch injury. The cell body of injured axons retained the ability to incorporate and transport horseradish peroxidase, but local interruption of axonal transport was demonstrated.[88] In a separate study, axonal injury was localized to the nodes of Ranvier and manifested as axolemmal blebs, loss of subaxolemmal density, loss of nodal gap substance, and neurofilament disarray.[84] Although distended, the axolemma remained intact. These findings suggest the possibility that stretch injury disrupts unidentified structural elements located at the node (i.e., membrane-associated proteins) that associate with the cytoskeleton and maintain nodal architecture. Furthermore, the study investigators speculated that nodal disruption leads to local cytoskeletal collapse and impairment of anterograde transport in a grossly intact axon.[84]

The cell ultrastructural events proceeding from axonal injury have been well characterized.[85] Continued anterograde transport to the site of focal impairment appears to result in localized ballooning of the axon and formation of a reactive axon bulb, or "Strich ball." Over the ensuing 1 to 3 days, the proximal axon segment containing the axon bulb continues to expand because of persistent anterograde transport and deposition of smooth endoplasmic reticulum and other intracellular organelles. These deposits become dispersed peripherally around an enlarged neurofilamentous core within the axon bulb. With further enlargement of the bulb, thinning of the overlying axolemma and myelin sheath occurs. Eventually, anatomic disconnection occurs between axonal segments proximal and distal to the original site of injury. The overlying myelin sheath is disrupted and then reforms to enclose the axon bulb, whereas the distal axonal segment undergoes Wallerian degeneration. Meanwhile, the proximal axon bulb continues to expand as a result of continued anterograde transport of intracellular contents from the neuronal soma. In rodent studies, by 14 days, most reactive axons degenerate, become electron dense, and are eventually phagocytized by microglia. By contrast, in studies of mild to moderate head trauma in cats, some reactive axons have been observed to undergo a regenerative process, with outgrowth of regenerative sprouts and growth cones.[89,90]

Axon cytoskeletal collapse and rapid loss of the microtubular network appear to underlie the observed impairment of axoplasmic transport after injury.[91] A quantitative analysis of injury-associated changes in the axoskeleton identified evidence of injury throughout the length of the axon: small axons demonstrated compaction of neurofilaments, larger axons demonstrated enlargement of the para-axonal space, compaction of neurofilaments, loss of microtubules, and reduction in axonal caliber. Neurofilaments have been implicated in maintenance of axon caliber, whereas microtubules are thought to provide the mechanism for fast axonal transport. Neurofilament compaction is thought to precede the cytoskeletal disappearance accompanying Wallerian degeneration. Collapse of neurofilaments into tightly packed bundles in the center of the axon may precede secondary axotomy in nondisruptive stretch injury of central nerves.[92] Injury-associated changes in the axonal cytoskeleton are preceded by alterations in axolemmal permeability. Intra-axonal accumulation of calcium has been demonstrated in focal spinal cord injury.[93-96] Increased calcium influx has been demonstrated in axons suffering stretch injury.[97] Using a guinea pig optic nerve model, a characteristic sequence of cellular events has been observed to occur over 24 hours. Initially, tensile strain leads to mechanical disruption of the myelin lamellae surrounding the nerve. Presumed loss of activity of the ecto-Ca-ATPase pump at sites of myelin disruption is then thought to allow increased calcium influx into the myelin, possibly mediating myelin dissociation, and increased periaxonal space over several hours. Increased calcium influx into the injured axon results in dephosphorylation of neurofilament side arms and proteolysis of neurofilaments.[98] In severe spinal cord injury, calcium-induced neurofilamentous degradation can be detected within 30 minutes.[99]

Abnormal strains in the spinal cord and brain stem from medullary kinking and basilar invagination result in predictable biomolecular changes: altered conformation of the Na+ mechanoreceptors is believed to cause increased intra-axonal Na^+. The increased Na+ results in depolarization of the voltage-gated Ca2+ channels and reversal of the Na+/Ca2+ exchange pumps, with the consequence of abnormal influx of Ca2+ and activation of a deleterious cascade of reactions (Fig. 20-4).[97,100-102]

Although increased calcium influx has been strongly implicated in neurofilamentous degradation by calcium-activated neutral proteases, some investigators question the relationship between calcium influx and the reactive axonal changes seen in stretch-related injury.[85] Povlishock[85] contends that neurofilamentous disarray is either a direct mechanical effect of trauma on the cytoskeleton or the result of increased neurofilament subunit exchange between stable neurofilaments and a pool of soluble kinetically active subunits. Although changes in axolemmal permeability and cytoskeletal disruption appear to trigger a cascade of intra-axonal changes in moderate to severe injury, in mild injury reactive axonal changes and retraction balls have been demonstrated in the absence of any change in axolemmal permeability and without evidence of neurofilament or microtubule loss. In these instances it has been speculated that a "focal misalignment" occurs at the time of injury, resulting in impaired axoplasmic flow and delayed axotomy.[103] Presumably, two different injury patterns exist, such that the specific mechanism of neuronal injury depends on the severity of tensile strain. In vitro studies have shown that axons under low tensile load undergo disruption of axoplasmic flow without evidence of axolemmal permeability change. On the other hand, high-tensile loading leads to immediate changes in axolemmal permeability and rapid disruption of axoplasmic flow.[104] Anatomically, axons appear to be disrupted at sites of maximal tension. Large-caliber axons with a long intra-axial course appear to be more susceptible to tensile injury.[66] Understandably, reactive changes are also seen where axons change course, cross blood vessels, and decussate.[105]

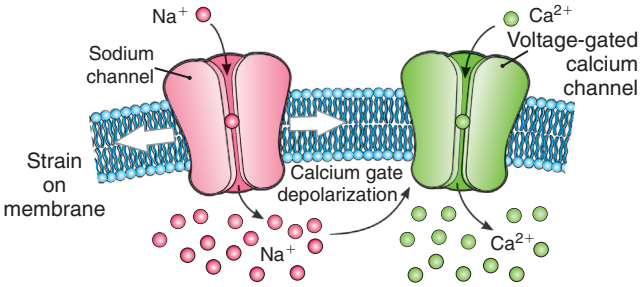

Figure 20-4. Mechanisms of calcium entry into stretch-injured axons. Strain on the axonal membrane opens mechanosensitive sodium channels, leading to an abnormal influx of Na^+. Influx of Na^+ and resulting depolarization opens voltage-gated calcium channels, leading to a pathologic influx of Ca^{2+} into the axons.

RELATIONSHIP BETWEEN ISCHEMIA AND SHEAR INJURY

Stretch injury renders axons more susceptible to secondary injury from other processes, including ischemia.[105] However, the role of ischemia in stretch-related injury is unclear. Reactive axonal swelling occurs against a histologic background that lacks strong evidence of ischemic change. Microscopic studies have failed to identify correlative changes in microvasculature or ischemia-related changes in the neuronal soma, axonal processes, or dendritic processes.[82] Iodoantipyrine studies have revealed no significant changes in regional blood flow.[106,107] Moreover, axons undergoing reactive change are frequently found surrounded by intact neurons, without any evidence of ischemia or injury. When axonal injury is observed near the soma, central chromatolysis has been observed but may be secondary to pathologic processes within the axon. The rapid onset of axonal changes weighs heavily against a process originating in the neuronal soma.

The fact that some axons undergo reactive change whereas immediately adjacent axons appear uninjured is difficult to explain. Povlishock[85] speculates that specific differences in axonal anatomy, such as location of intra-axial turns, may make certain axons uniquely susceptible to injury at specific levels. In the peripheral nervous system, axonal swelling can be seen in response to various insults (e.g., ischemia, severance, and crushing).[85] Caution must be used before assigning a given etiology to the morphologic finding of axonal swelling.

APOPTOSIS

The pathogenesis of myelopathy is beginning to be investigated on a molecular level. Studies suggest that a significant portion of cell loss in chronic compression-related myelopathy is caused by apoptosis.[108] The process of apoptosis is biologically distinct from necrosis and refers to a well-defined sequence of intracellular events that are characterized by internucleosomal chromosome fragmentation, membrane blebbing, and phagocytosis, without generation of an inflammatory response.[109] In contrast, cell necrosis typically involves random DNA cleavage, membrane disruption, mitochondrial swelling, and local inflammation.[110] Although necrosis and apoptosis often occur concurrently, identifying the dominant biologic process can provide important insight into the causes of specific disorders. In the case of CSM, the identification of primarily apoptotic cell death is significant. Although ischemia is one of numerous triggers associated with apoptotic cell death, severe ischemia such as that implied in the pathogenesis of CSM is more characteristically thought to cause cell death through necrosis. Therefore, the fact that oligodendrocyte disappearance in CSM appears to be apoptotic in nature suggests that a mechanism other than pure ischemia is involved.[111] A prominent role for apoptosis has already been implicated in the secondary cell loss that occurs after traumatic spinal cord injury.[111-115]

Cell loss occurs in spinal cord injury, both at the time of injury and secondarily over a period of days to weeks. At the injury epicenter, most cell death occurs through necrosis and leads to active clearance of necrotic cell debris through macrophage and microglial phagocytosis.[116] However, white matter cell loss continues through a longer segment of the spinal cord for several weeks in a process called *secondary injury*. Animal studies have demonstrated that compressive cord injury leads to apoptosis of oligodendrocytes along degenerating white matter tracts.[111,113] These studies indicate that apoptosis begins within 24 hours of injury and continues for at least 3 weeks.

Strong evidence for the occurrence of apoptotic cell death in chronic compression-related cervical myelopathy comes from studies of an animal model of chronic compression-related cervical myelopathy, the tiptoe-walking Yoshimura mouse.[117] The Yoshimura mouse is an inbred strain that characteristically develops quadriparesis 4 to 8 months after birth because of severe spinal cord compression, a result of hyperostosis along the posterolateral margins of the C1 and C2 vertebrae.[118] Histopathologic examination of cord tissue from Yoshimura mice has demonstrated descending degeneration affecting the anterior and lateral columns, ascending degeneration along the posterior columns, as well as severe injury at the level of compression.[108] Glial cell apoptosis mirrored the pattern of white column degeneration. Histologic staining using cell type-specific markers confirmed that the apoptotic cells were oligodendrocytes. The study investigators also performed an autopsy of a patient with cervical myelopathy from ossification of the posterior longitudinal ligament and reported discovering a similar pattern of neuronal loss, demyelination, and apoptosis.

Stretch and strain are major epigenetic factors in trauma. For example, stretch results in the up-regulation of *N*-methyl-d-aspartate receptors. This renders the neuron more susceptible to ischemic insults and the effects of nitrous oxide and free radical species.[119]

NEW TECHNOLOGY: DIFFUSION TENSOR TRACTOGRAPHY

Diffusion tensor imaging (DTI) is now being assessed as an in vivo imaging tool for evaluating microstructural change in the setting of chronic spondylotic myelopathy. Nerve injury results in altered diffusion; the orientation and strength of diffusion is represented by three vectored eigenvalues, which are used to generate diffusion tensor metrics: fractional anisotropy (FA), axial diffusivity; and radial diffusivity. Quantification begins with the construction of fiber bundles using tractography algorithms. Cui and colleagues[120] used DTI metrics within the tracts to quantitate column-specific degeneration. They found that the microarchitectural integrity of the posterior and lateral columns were significantly decreased in the patients with cervical spondylotic myelopathy, as compared to healthy controls. Furthermore, they demonstrated that FA could be used to quantitate a difference between the pathologic side of the spinal cord and the normal side in a case of a more subtle pathologic insult. With further refinements, fiber tractography may have potential for in vivo measurement of disease progression.

SUMMARY

The presence of cervical spine mobility, instability, and kyphosis is strongly predictive of clinical progression in patients with CSM. The cervical spinal cord may be subject to abnormal deformative stresses by spondylotic transverse bars, abnormal cervical kyphosis, deformity at the level of the craniocervical junction due to basilar invagination or abnormal CAA, or by remote tethering of the cord. Both proximate and remote tensile and shear forces generate deformative stresses that alter the biomolecular milieu through the Na^+ and Ca^{2+} channels and disrupt axoplasmic transport through alteration of the intra-axonal architecture, thereby modulating the electrophysiology of the nerve conduction in general and causing pain and decreased neurologic function. Dynamic mechanical stresses appear to alter genetic expression.

Strong support for the shear and strain injury model of CSM pathogenesis comes from the clinical concept of "dynamic stenosis," an increased neurobiologic understanding of the pathophysiology of stretch-related myelin and axonal injury, insight into the pathogenesis of spinal cord tethering, histologic studies revealing reactive axonal injury in the spinal cord of patients with CSM, and mathematical and finite element analysis modeling of the neuraxis under conditions of deformative stress.

Axonal injury reproducibly occurs at sites of maximal tensile loading. Mechanical injury to the neuronal axon triggers a well-defined sequence of intracellular and paracellular events. Myelin stretch injury leads to changes in axolemmal permeability. Histologically, cytoskeletal collapse is observed in neural cells in association with alterations in anterograde and retrograde axonal transport. Eventually, delayed axotomy occurs. The stretch and shear model may account for the clinical presentation and recovery potential of milder forms of CSM. Of more importance, a greater understanding of the deleterious effects of stretch and shear on the cervical spinal cord may improve treatment strategies for CSM and other spinal cord injuries.

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