Pathophysiology of cervical myelopathy (Review)

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Abstract. Cervical myelopathy is a well-described medulla spinalis syndrome characterized by sensory disorders, such as pain, numbness, or paresthesia in the limbs, and motor disorders, such as muscle weakness, gait difficulties, spasticity, or hyperreflexia. If left untreated, cervical myelopathy can significantly affect the quality of life of patients, while in severe cases, it can cause disability or even quadriplegia. Cervical myelopathy is the final stage of spinal cord insult and can result from transgene dysplasias of the spinal cord, and acute or chronic injuries. Spondylosis is a common, multifactor cause of cervical myelopathy and affects various elements of the spine. The development of spondylotic changes in the spine is gradual during the patient's life and the symptoms are presented at a late stage, when significant damage has already been inflicted on the spinal cord. Spondylosis is widely considered a condition affecting the middle aged and elderly. Given the fact that the population is gradually becoming older, in the near future, clinicians may have to face an increased number of patients with spondylotic myelopathy.

Contents

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1. Morphology

The vertebral column is the structural base of the human body. It comprises complex bony elements (vertebrae) and soft fibrous elements (intervertebral discs and ligaments). The key anatomical parts of the vertebrae are the vertebral body, the pedicle, lamina, the spinous process and the transverse process in the thoracic and lumbar parts of the spine. The intervertebral disc is located between the vertebral bodies. The zygapophyseal and Luschka joints are the primary joints that contribute to the maintenance of the vertebral column's architecture during static position and motion. Finally, various fibrous ligaments, such as the anterior and posterior longitudinal ligaments and the ligamentum flavum, contribute to the maintenance of spinal cord structure. Each part of the vertebral column has unique biochemical and functional characteristics; however, they all articulate with each other in order to for the body to be able to make complex and delicate movements (1,2).

The intervertebral disc is the most critical and extensively investigated structure of the soft tissues of the vertebral column. It is placed between the un-elastic and non-compressed bodies of the vertebrae and sustains multi-direction compressive, bending, or shearing forces (1,2) during body motion or posture sustenance. However, the acting forces over the spine are not distributed equally over the intervertebral discs, leading to more significant wear of the most stressed parts of the disc. The reasons for that are some anatomical characteristics of intervertebral disc components (e.g., eccentric location of nucleus pulposus in the disc) and the fact that the spine sustains multi-direction loads (3).

The intervertebral disc is separated into two parts: The outer part is the annulus fibrosus, while the inner part is the nucleus pulposus. Furthermore, the annulus fibrosus is subdivided into an external zone consisting of complex collagen type I fibers and an internal area composed of soft collagen type II fibers (1,2). The external zone of the annulus fibrosus bridges two successive vertebral bodies. In addition, due to its architecture and biochemical characteristics, the annulus fibrosus functions similar to a diffusion filter that controls the

crossing of fluids, ions and macromolecules between articular plates and intervertebral discs (4).

The nucleus pulposus is a gel-like formation composed mainly of glycosaminoglycans and water (1,2). It is located approximately in the middle of the distance between the central and posterior parts of the intervertebral disc (5). In the case that a static compressive load is forced on the intervertebral disc, the nucleus pulposus loses some of its water content and its height is reduced. When the pressure from this load is terminated, the nucleus pulposus retains the lost moisture and regains its original size. In the case that a shear load is inflicted on the intervertebral disc, the nucleus pulposus can move inside the annulus fibrosus, consuming the load. The nucleus pulposus retains its original location inside the disc when the pressure of the load is terminated.

This difference in the biochemical structure of the annulus fibrosus and nucleus pulposus is fundamental to their unique functionality. Thus, the annulus fibrosus, with its high content of fibers, serves to stand tension, shear and torsion, while the nucleus pulposus, with its high content of proteoglycans, serves to stand compression forces (6-8). In conclusion, the intervertebral disc acts functions as an elastic jolt absorber under multi-axial loads.

Two continuous vertebrae are linked with a pair of joints known as the zygapophyseal. These are accurate joints containing articular plates, articular cartilage and synovial tissue, and bridge the faceting process of two continuous vertebrae. Apart from their connecting role, zygapophyseal joints participate in the motions of the spine and sustain a part of the loads that act over the spine. Similar to intervertebral discs, zygapophysial joints are designed to sustain multi-axial compressive (9) and shear (10,11) loads. Additionally, zygapophyseal joints stabilize other parts of the spine's soft tissues, particularly the upper vertebral column (12).

On the lateral side of the cervical intervertebral disc, the annulus fibrosus is subdivided by transverse clefts (13,14). These clefts are not anatomical formations that exist in the fetus, but develop later in the child's life and become more profound in adulthood (15,16). Later on in adult life, a joint pseudocapsule is formed inside the fissures (1,2), and the formed joint is known as the uncovertebral or Luschka joint (13,14). However, the exact formation mechanism of these fissures remains to be determined. In various models, it has been found that the clefts are formed in the intervertebral disc area, where the highest load pressure acts (12,17,18). On the contrary, the role of Luschka joints is well known. They cooperate with facet joints to perform lateral bending and axial spine rotation (19). Furthermore, Luschka joints restrict extreme movements of the spine (7,20), avoiding possible damage.

Finally, various fibrous ligaments connect two or more continuous elements of the vertebral column. These ligaments are generally high-percentage elastin and collagen structures and are designed to resist tensile and destructive loads (7). Their exact function depends on their biochemical characteristics and the spinal parts they connect. Ligaments with a high concentration of elastin have a more elastic function (21,22), whereas ligaments with a high percentage of collagen have a more stabilizing role. Furthermore, the complex entheses of spine ligaments render them capable of resisting multiple loads, although they are most effective when distracted along the direction of the fibers (23). The critical ligaments of the spine are described below:

The anterior longitudinal ligament is located on the ventral side of the spinal cord and binds the bodies of the vertebrae. Due to its location, the anterior longitudinal ligament limits the extension of the spine (23).

The posterior longitudinal ligament binds the dorsal part of the vertebral bodies. Due to its caudal location, it limits the flexion of the spine. On the other hand, as the posterior longitudinal ligament is located close to the center of rotation, it is not as effective against loads during rotation (12).

Interspinous ligaments connect the vertebral processes of the spine. Mainly, they are composed of collagen fibers, as 5-20% of them are comprised of collagen (24,25). Therefore, their main role is to limit the flexion of the vertebral column (25). Additionally, these ligaments cooperate with the anterior longitudinal ligament and resist the applied forces during rotation.

The ligamentum flavum is located in the posterior part of the laminae. It is the most elastic tissue of the body, with a collagen/elastin ratio of 1/4 (26,27). Its main role is to maintain the vertical posture of the spine and assist the vertebral column in resuming it after flexion.

Capsular ligaments connect the inferior articular process of a vertebra with the superior process of the lower vertebra (28). They serve as local stabilizers of the zygapophyseal joint (28,29), particularly during rotation (28).

2. Pathophysiology

Intervertebral discs, joints and ligaments have a poor or absent feeding vascular network. As a result, the nutrition of the intervertebral discs is covered mainly through a vascular network that penetrates only to the outer zone of the annulus fibrosus and through diffusion from vertebral end plates (30). Additionally, fluids and elements of nutrition enter the intervertebral disc during the movements of the spine. When the disc is compressed, it loses water through a mechanism which is discussed below. When the compression stops, the disc retains its original height, absorbing fluids and nutrients with a mechanism similar to a pump.

This lack of blood vessels inside the nucleus pulposus, the inner part of the annulus fibrosus and the articular cartilage does not only have negative effects. The architecture of the aforementioned structures appears to be more solid without penetrating vessels, rendering them more effective in resisting loads (31).

The harmonic cooperation of the vertebrae, the intervertebral discs, the small joints and the ligaments renders the vertebral column capable of sustaining multiple external forces, such as compression, shear and rotation during the static or dynamic posture of the body. Additionally, it contributes to maintaining the architectural integrity and functionality of the vertebral column during and after the force stops acting.

Cervical spondylotic myelopathy (CSM). Cervical myelopathy is a well-described medulla spinalis syndrome characterized by sensory disorders, such as pain, numbness, or paresthesia in the limbs, as well as motor disorders, such as muscle weakness, gait difficulties, spasticity, or hyperreflexia. Pathologically,

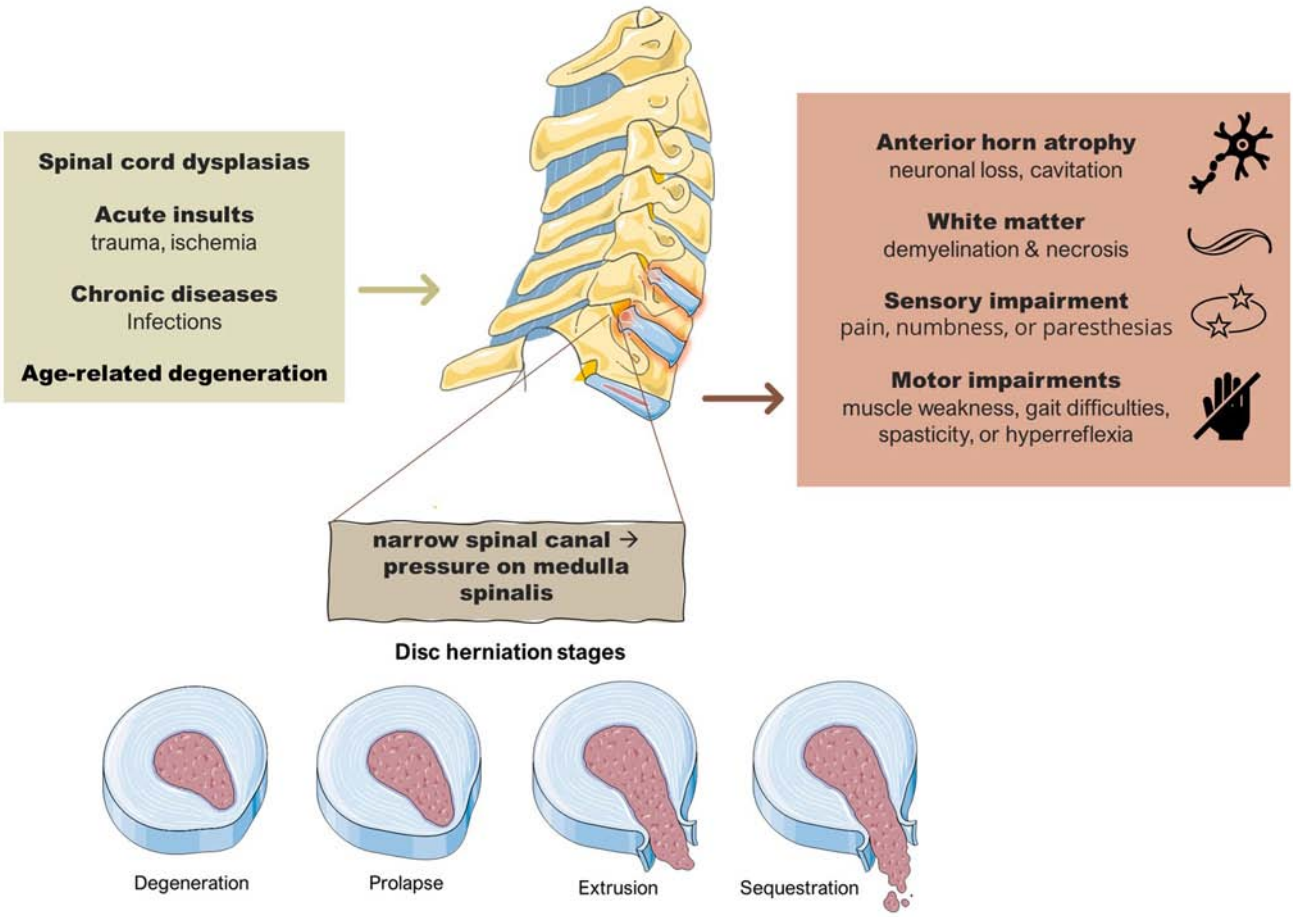

Figure 1. Cervical spondylotic myelopathy: Cervical vertebral column with herniated discs, causative factors, pathophysiological mechanisms and consequences and stages of disc herniation; please refer to the text for details. Parts of this image was derived from the free medical site, http://smart.servier.com/ (accessed on September 13, 2023) by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.

myelopathy is characterized by atrophy of the anterior horn (32) and loss of the neurons in the gray matter, with accompanying cavity formation within the gray matter. By contrast, in white matter, demyelination, necrosis (33), myelin pallor,and atrophy can be encountered (33,34). A summary of the underlying causes, mechanisms and consequences of this condition is illustrated in Fig. 1.

Cervical myelopathy can result from transgene dysplasias of the spinal cord, acute insults, such as trauma or ischemia, and chronic issues such as infections and age-related degeneration of the spinal cord. Spondylosis is a multifactorial (genetic deformation, aging deterioration and loading history) (35) cause of cervical myelopathy and affects various elements of the spine like vertebrae, intervertebral discs, joints and ligaments. Spondylosis is characterized by multi-type vertebral column deformations, such as the formation of bony spurs, the degeneration of facet and Luschka joints (32), the calcification of soft tissues and ligaments, and the degeneration of the intervertebral disc. The outcome of all these deformations is a profoundly narrow spinal canal (36,37), which causes direct pressure on the medulla spinalis. Additionally, it has been shown that the chronic degeneration of the spine causes the static compression of the spinal medulla. The dynamic compression that occurs during the movements of the spine can cause cervical myelopathy (38,39). Finally, ischemic deterioration appears to be induced during aging and contributes to the development of myelopathy (33,34).

Spondylosis is widely considered a condition affecting middle-aged individuals; 95% of asymptomatic males and 70% of asymptomatic males by the age of 60-65 years have signs of degeneration in cervical radiography (38), and 57% of asymptomatic individuals >40 years of age have disc degeneration, while 40% of the individuals in the same age group have bone spurs in a cervical MRI (40), whereas only 10% of individuals by the age of 25 have spondylotic deformations (41).

Age deterioration. During the first years of life, the vertebral column is at the peak of its morphological integrity and functionality. As the years progress, a number of age-related changes occur in the spine. These changes, along with spinal deformations which occur due to acting loads, disrupt the architecture of the vertebral column and deteriorate its functionality.

The intervertebral disc, as aforementioned, is an avascular structure that meets its needs for fluids and macromolecules through the vascular network of the outer annulus fibrosus and diffusion from the surrounding tissues. More specifically, when a load compresses the disc, water is drained out, increasing the osmotic pressure inside the disc and decreasing the height of the disc. When the load stops acting, the high osmotic pressure in the disc drives the lost amount of water back to the

nucleus pulposus and the disc back to its original height. The disc of a young individual contains an increased number of proteoglycans and only a small amount of fiber, and thus it has an enhanced ability to absorb water. In summary, during youth, the biochemical structure and the proper function of the intervertebral disc, in combination with the integrity of the annulus fibrosus vascular network, guarantee the proper supplementation of the disc (31).

During aging, the biochemical composition (42) and the architecture of the intervertebral disc change significantly. The biochemical changes involve the shift of chondroitin-4-sulfate, chondroitin-6-sulfate and keratan sulfate, which are the main glycosaminoglycans in the intervertebral disc of a young individual, to dermatan sulfate (31). The changes which occur in the glycosaminoglycans, and amounts and quality of proteins I the disc during aging reduce the quantity of water inside the disc.

As a result, the disc height is reduced (1) and it becomes an unelastic and fibrous structure (41). Additionally, melanin-like molecules are collected inside the nucleus pulposus, and the disc thus acquires a dark brown shade (43). Architectural changes occur in the first years of adult life. They involve multiple tears and fissures that develop on the lateral surface of the annulus fibrosus and progressively extend to the nucleus pulposus (1,44). Due to its biochemical and structural changes, these gap formations result from the reduced capacity of the disc to carry loads (44).

Furthermore, nutrient supply to the avascular disc becomes less efficient in a spine from an older individual. As a result, the poorly supplied intervertebral disc has a low regeneration rate. This fact reduces the ability of the disc to repair the damage from mechanical loads (45).

The aging procedure affects the intervertebral disc and the surrounding cartilage formations. Namely, the amount of proteoglycans in cartilage is reduced over time (46), reducing the ability of the cartilage to maintain an adequate amount of water, and making it less elastic. Additionally, the connection between the collagen fibers alone (47) and the collagen and sugar molecules become tighter, increasing the inelasticity of the spine.

In summary, during the first years of adulthood, intervertebral discs and the surrounding cartilage domains become stiffer, the height of the disc decreases, and the amount of water inside the disc is reduced, rendering the poorly supplied disc unable to sustain multi-direction loads (35). The changes described above, which are early deteriorations observed over the spine, are known as intervertebral chondrosis (1).

In the following years of adult life, more deteriorated detriments accumulate over the spinal cord. During this stage, the percentage of intra-disc water is further reduced, causing a significant downside to the intervertebral disc compared with the stage of intervertebral chondrosis (1). In addition, the nucleus pulposus and the internal part of the annulus fibrosus are the most affected during this stage. By contrast, the outer part of the annulus fibrosus is less affected. As a result, internal part of the disc prolapses through the healthier outer part of the annulus fibrosus (1).

Apart from the intervertebral disc, cartilage and spongiosa are affected at this stage. The reason is that the degenerated disc does not function sufficiently, and some acting loads are forced onto the adjacent structures of the disc. This causes a disorder of the natural architecture of the cartilage endplates and the formation of ossification, while the vertebral spongiosa becomes sclerotic and thicker (1). This second stage of spinal degeneration is termed intervertebral osteochondrosis.

As aforementioned, the intervertebral disc is an avascular formation. Nonetheless, during the aging procedure, newly formed blood vessels penetrate the nucleus pulposus through the tears of the annulus fibrosus or the end plates of the vertebrae (48,49). The exact mechanism of the deployment of blood vessels remains to be determined. High-quantity glycosaminoglycan formations, such as intervertebral discs resist the deployment of new vessels. During aging, the quantity of glycosaminoglycans is reduced in the intervertebral disc, allowing them to penetrate new vessels. Angiogenesis may be a potential repair mechanism of the spine for age-related degeneration (31) or the outcome of reduced levels of glycosaminoglycans. The only confirmed fact is that the penetration of blood vessels inside the nucleus pulposus changes its structure. The expression of metalloproteinases near the newly developed vessels of the intervertebral disc can contribute to these changes (50).

All the age-related changes in the architecture of the vertebral column described above affect its stability and efficiency in resisting forces during standing or body movements. The degenerated intervertebral disc cannot stand the loads during acting, inflicting an increased load stress on the adjacent articular cartilage of vertebrae and their end plates (44). To reduce the instability of the spine, multiple bony particles (osteophytes) are formed (51) at the edge of the vertebrae. Lamellar bone covers osteophytes, which have spongiosa similar to that of the vertebrae (52). These osteophytes increase the area of the area that sustains the compression and make the arthrosis more stable. Spondylosis deformations enhance this effect, and osteophytes are common in the more mobile cranial part of the cervical spine. At the same time, they are uncommon in the caudal part (53,54).

While the formation of osteophytes is a well-known defense mechanism to stabilize degenerated arthrosis, the exact mechanism of osteophyte formation is controversial. Schmorl's first model postulates that the fissures and tears in the outer zone of the annulus fibrosus make the intervertebral disc complex, and the nearby vertebral bodies more unstable and susceptible to pathological movements. The outcome of these movements is that the anterior longitudinal ligament sustains an increasing load, which is transferred to ligament insertions on the surface of vertebral bodies. Additionally, the intervertebral disc presses the anterior longitudinal ligament during these movements, increasing the tension at the ligament insertions. The outcome of this continuous stress is the formation of osteophytes at the insertions of the anterior longitudinal ligament (55). The second model, described by Collins (56), proposes that the fissures and tears in the outer zone of the annulus fibrosus are the ports through which tissue from the degenerated disc penetrates out of the nucleus puplosus. During this time, the collected penetrating disc tissue near the vertebrae edges is ossified, resulting in the formation of vertebrae body osteophytes (56). In summary, both models propose that the anterior longitudinal ligament plays a key role in the formation of osteophytes. This is unusual, considering

that the common location where osteophytes are formed is the ventral surface of the vertebrae just caudally to the vertebrae edges, a location where the anterior longitudinal ligament is not sufficiently strong (53).

The sum of all age-related spine deformations affects not only the intervertebral disc, but also the joints of the spinal cord. Osteochondrosis of the vertebral end plates and intervertebral discs alters the segmentation of the acting loads (44). In addition, the joint is forced to participate in a greater range of movements (57) due to the instability caused by the degeneration of the spine (51). These structural changes, combined with hypermobility, are believed to induce the formation of tears in cartilage and osteoarthritis-like deformation of the facet joints. Additionally, intense sclerosis is found in the subchondral formations, while the final step of degeneration is the hyalinization of the zygapophyseal joints and the formation of osteophytes (52).

Furthermore, due to the change in load segmentation, uncovertebral processes and Luschka joints are forced to resist higher forces (44), resulting in the flattening of uncovertebral processes (1,44). The load segmentation change, in combination with the flattening of uncovertebral processes, increasing the load on the articular cartilage and the adjacent end plate of the vertebrae (44), inflicting further damage to these structures. Additionally, the flatter uncovertebral processes are a potential place for osteophyte formation (52). These osteophytes can grow in the direction of the transverse foramen and compress the vertebral artery, particularly during extreme neck movements, causing severe hypoperfusion to the cervical part of the medulla spinalis (58).

Finally, the overgrowing osteophytes can compress the ligamentum flavum, bending it and making it harder (59). This bent ligamentum flavum can inflict direct pressure on the medulla spinalis and the vertebral artery, causing lesions to the spinal cord due to pressure or hypoperfusion.

Canal size. The medulla spinalis is a delicate neural formation inside a protective cage known as the spinal canal of the vertebral column. The size of the spinal canal differs along the spinal cord or among the sexes (males appear to have a wider canal in all the cervical segments compared with females) (60). The wider part is located in the lumbar spine, while the diameter of the spinal canal is reduced when during cranial movements. The anteroposterior diameter of the canal between C3 and C7 segments has been reported to be 17-18 mm (61,62), while other reports have demonstrated a decrease to the considered normal sagittal diameter of the canal to 14.1±1.6 and 13.73±1.37 mm (60,63).

Various researchers have reported that spinal canal stenosis is a key factor predisposing to the development of the direct compression of the medulla spinalis and cervical myelopathy (38,63,64). The fact that individuals with congenital canal stenosis are more susceptible to cervical myelopathy (65,66) supports this theory. Moreover, the size of the cervical canal is considerably reduced in patients with cervical myelopathy compared with healthy individuals (37,67). By contrast, myelopathy symptoms are more severe in patients with a considerably decreased canal size (63). Direct measurements in patients and cadavers have demonstrated that a compromise of the canal's acreage <60 mm^2 (68) or the canal's sagittal diameter <13 mm (69) is associated with an increased possibility of developing cervical myelopathy (37,44). On the other hand, individuals with a canal diameter between 13 and 17 mm have a reduced possibility of developing myelopathy. However, they can still present signs of cervical spondylosis, and individuals with a canal diameter >17 mm will not develop cervical spondylosis (37).

Spondylosis, as aforementioned, is the spinal cord's normal aging procedure and includes a group of changes, such as the deterioration of the intravertebral disc, the hypertrophy and ossification of the spine's ligaments, and the formation of osteophytic spurs (32,70). These changes compromise the size of the spinal canal, inflicting direct pressure on the medulla. Chronic pressure is a predisposing factor for developing CSM (32,44,70). Moreover, when spondylosis and congenitally narrowed canals coexist, the possibility of developing CSM increases (44).

Dynamic compression. Although the model described above appears sufficient, it fails to explain the onset of myelopathy in patients with minimal compromise of the spinal canal and the absence of symptoms in healthy individuals with spinal canal stenosis (71,72). Moreover, cervical myelopathy increases in incidence in individuals with extreme or unphysiological neck movements (64,71,73-75). Subsequently, static compression of the medulla from spondylotic formations does not appear to be the unique pathophysiological model that describes spondylotic myelopathy.

To explain that paradox, the motion physiology of the spinal cord needs to be studied. During normal flexion and extension, the morphology of the spine is altered, affecting the diameter of the spinal canal (76,77). In flexion, the spinal canal is elongated, and the spinal cord is stretched, inducing axial tension (72,76). Typically, the cervical and lumbar spine are the most mobile parts of the spinal cord; thus, it is logical that the white and grey matter of these spine parts are stressed the most (78,79). In extension, the spinal canal is narrowed due to the shingling of the laminae and buckling of the ligamentum flavum, while the spinal cord itself becomes shorter and thicker (42,76). Additionally, during a shift from flexion to extension, the bulging of the intervertebral discs and ligamentum flavum decreases the diameter of the spinal canal (80). Moreover, the canal is compressed by intervertebral discs and ligamentum flavum bulging when a load is inflicted upon the spinal cord. These modifications of the architecture of the spine during motion inflict direct pressure on the cervical medulla (81), and are predisposing factors for the development of CSM. The observation advocates the theory that extreme cervical spine movements are associated with progressive CSM (73-75). An additional supporting argument is that surgical decompression and stabilization of the spine, which decrease the pressure over the cord and eliminate the abnormal motion, improve the clinical status of patients with CSM (82-85).

Of note, age-related degenerative changes in the spine exacerbate the dynamic compression of the cord. In flexion, the spinal cord can be farther stretched over anterior osteophytes or calcified herniated discs, while in extension, the buckling ligamentum flavum compresses the cord (69,86). As previously demonstrated in a clinical protocol, the cord's

compression during motion by ventral osteophytes can induce chronic stretching and shear injury to the dorsal cord (87). This fact supports the theory that dynamic compression, in combination with spondylosis, is a predisposal factor for developing CSM. Moreover, age-related changes in the spine can induce cord pressure and, consequently, CSM through local tethering action. In individuals with no spondylosis, the strain during motion of the vertebral column is split over the entire spinal cord. By contrast, in individuals with spondylotic deformation, the strain is focused adjacent to age-related formations (72). A potential explanation is that spine ligaments induce tethering stress over the cord in areas near spondylotic deformations during flexion and extension (72).

Ischemia. The notion that ischemia contributes to the development of CSM is not a new one, but remains controversial. Numerous protocols support this theory. Specifically, the anterior spinal artery and parenchymal arterioles present pathological changes, such as vessel wall thickening and hyalinization (88,89). By contrast, radicular artery diameter is affected by the fibrosis of intervertebral foramina in patients with CSM (90). Additionally, histopathological clues of ischemic injury over the grey and white matter of the spine have been observed in patients with CSM (76,91).

A pathophysiologic explanation is that time-related degenerative formations of the cervical spine can compress major feeding arteries such as the vertebral arteries (33), the anterior spinal artery and its ventral branches, or the radicular arteries of the neuroforamina (73,89). As a result, the blood flow velocity within the vertebral artery can be abnormally reduced (92), while blood perfusion to vital parts of the spinal cord is compromised (93). Moreover, spondylotic deformities can compress the venous outflow of the spine, reducing blood drainage from the spine (73,89). Various studies on humans and animals support this hypothesis. The outcome of a canine study where terminal branches of the anterior spinal artery and penetrating branches of the lateral pial plexus are curved and stretched around degenerative formations of the spine was a decrease in blood flow to corticospinal tracts (94). Additionally, angiography studies on animal models suffering from CSM have revealed signs of ischemia (95,96). Other researchers have examined the simultaneous insult of direct compression and ischemia to the cord. In detail, ischemia appears to enhance the injury due to the anterior compression over the medulla (94), changing blood flow to the spinal cord (97). In this protocol, corticospinal tracts are the most affected part of the medulla (94), which has also been found in patients with CSM (69). In another experimental protocol, the direct compression of specific spine arteries causes a decrease in blood flow to the respective artery's feeding part of the spine (98).

On the other hand, there are some clinical and experimental protocols that fail to associate ischemia with CSM. In detail, patients or laboratory animals with moderate CSM have no (99) or only mild signs of ischemia (100,101). By contrast, pathological evidence of ischemia has only been found when severe canal stenosis coexists (102,103). Moreover, some experimental studies have only found minor changes in blood flow during compression and decompression (79,104).

3. Conclusion

Spondylosis is a multi-factor cause of cervical myelopathy. The onset of CSM-related symptoms is insidious and if left untreated, it can cause severe disability in affected patients. Given the fact that spondylotic changes take time to be developed and that the population is gradually becoming older, CSM will be one of the most common health issues among elderly patients in the future. A better understanding of the mechanism that drives to the formation of spondylotic changes will aid in the development of more effective treatment and preventive strategies.

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Authors' contributions

GF and KF conceptualized the study. IGL, VEG, PP, NT, PS, GF, KF and DAS made a substantial contribution to the interpretation and analysis of the literature data to be include in the review, and wrote and prepared the draft of the manuscript. GF and KF analyzed the data from the literature for inclusion in the review and provided critical revisions. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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