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DEGENERATIVE CERVICAL SPINAL STENOSIS: BIOMECHANICAL AND MOLECULAR FOUNDATIONS OF CERVICAL MYELOPATHY PATHOGENESIS

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RESUME

Degenerative cervical spinal stenosis, accompanied by cervical myelopathy, represents a leading cause of spinal cord dysfunction in adults. Contemporary insights into the pathogenesis of this condition, which integrates biomechanical, vascular, and molecular mechanisms, highlight its multifactorial etiology. Chronic spinal cord compression, driven by osteophytes, hypertrophic ligaments, and disc herniations, synergizes with dynamic mechanical stresses, culminating in ischemia, disruption of the blood-spinal cord barrier (BSCB), and neuroinflammation. Central to the pathogenesis is chronic hypoperfusion, exacerbated by excitotoxicity and activation of matrix metalloproteinases (MMP-9, MMP-2), which degrade the vascular basement membrane. BSCB breakdown facilitates immune cell infiltration, release of pro-inflammatory cytokines (TNF- α , IL-1 β), and microglial activation via the CX3CL1-CX3CR1 signaling axis. These processes trigger apoptosis of neurons and oligodendrocytes, leading to demyelination and spinal cord atrophy. Special emphasis is placed on the role of acetylation processes (involving NAT1, NAT2, AANAT, and NAA20 gene expression) in Ligamentum flavum ossification, underscoring the influence of genetic factors and gender disparities. This review addresses unresolved questions, including variability in clinical manifestations, the contribution of metabolic and immune dysregulation, and the urgent need for neuroprotective strategies. The integration of these innovations may bridge current knowledge gaps and improve outcomes for patients with degenerative cervical myelopathy. A systematic literature review (2010–2024) was conducted using PubMed, Scopus, Google Scholar and Cochrane Library. Search terms included degenerative cervical myelopathy, spinal stenosis, BSCB disruption, neuroinflammation and acetylation mechanisms. Inclusion criteria prioritized clinical/preclinical studies and meta-analyses exploring pathophysiology and therapeutic innovations. Data were analyzed thematically. The aim of the study is to analyze and synthesize existing knowledge on the pathogenesis of degenerative cervical myelopathy.

Key words: cervical spinal stenosis, cervical spondylotic myelopathy, pathogenesis of cervical myelopathy, neuroinflammation, gene acetylation

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ПАТОГЕНЕЗ ДЕГЕНЕРАТИВНОЙ ШЕЙНОЙ МИЕЛОПАТИИ: ОТ БИОМЕХАНИКИ К МОЛЕКУЛЯРНЫМ МЕХАНИЗМАМ

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РЕЗЮМЕ

Дегенеративный стеноз шейного отдела позвоночника, сопровождающийся шейной миелопатией, является ведущей причиной дисфункции спинного мозга у взрослых. Современные представления о патогенезе заболевания, объединяющем биомеханические, сосудистые и молекулярные механизмы, подчеркивают многофакторный характер его этиологии. Хроническая компрессия спинного мозга, вызванная остеофитами, гипертрофированными связками и грыжами межпозвонковых дисков, сочетается с динамическими нагрузками, приводя к ишемии, нарушению целостности гемато-спинномозгового барьера (ГСМБ) и нейровоспалению. Ключевым звеном патогенеза выступает хроническая гипоперфузия, усугубляемая эксайтотоксичностью и активацией матриксных металлопротеиназ (MMP-9, MMP-2), разрушающих сосудистую базальную мембрану. Нарушение барьера способствует инфильтрации иммунных клеток, выбросу провоспалительных цитокинов (TNF- α , IL-1 β) и активации микроглии через сигнальный путь CX3CL1-CX3CR1. Эти процессы запускают апоптоз нейронов и олигодендроцитов, приводя к демиелинизации и атрофии спинного мозга. Особое внимание уделено изучению роли процессов ацетилирования (экспрессия генов NAT1, NAT2, AANAT, NAA20) в развитии оссификации *Ligamentum flavum*, и значению генетических факторов и гендерных различий. Обзор акцентирует внимание на нерешенных вопросах: вариабельность клинических проявлений, роль метаболических и иммунных факторов, а также необходимость разработки нейропротективных стратегий. Обзор литературы был проведен с использованием баз данных PubMed, Scopus, Google Scholar и Cochrane Library за период с 2010 по 2024 гг. Поисковые термины включали: стеноз шейного отдела позвоночника, спондилогенная миелопатия, патогенез шейной миелопатии. При написании работы приоритет отдавался клиническим/доклиническим исследованиям и метаанализам, изучающим патофизиологию и терапевтические инновации. Данные анализировались тематически. Цель исследования – проанализировать и обобщить существующие знания о патогенезе дегенеративной шейной миелопатии.

Ключевые слова: стеноз шейного отдела позвоночника, спондилогенная миелопатия, патогенез шейной миелопатии, нейровоспаление, ацетилирование генов

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INTRODUCTION

Degenerative cervical spinal stenosis is a complex, multifactorial disease caused by dystrophic processes in the spine that lead to the narrowing of the spinal canal and the manifestation of clinical symptoms. One such condition is cervical myelopathy, which is the most common cause of spinal cord dysfunction in adults [1, 2, 3]. Degenerative changes in the cervical spine, including the formation of osteophytes, herniated intervertebral discs, and thickened ligaments, can lead to chronic compression of the spinal cord, resulting in varying degrees of neurological impairment. The prevalence of the disease increases with age, and it is estimated that up to 2 % of the adult population suffer from compressive myelopathy, with an annual incidence of approximately 4 cases per 100,000 people [1]. Clinical manifestations of cervical myelopathy can range from numbness and weakness in the extremities to gait abnormalities, impaired coordination, dysfunction of pelvic organs, and, in severe cases, tetraparesis and tetraplegia [1]. These symptoms can significantly reduce patients' quality of life and lead to disability. Therefore, timely diagnosis and a thorough understanding of the underlying causes of the condition are of crucial clinical importance.

The significance of researching the pathogenesis of spinal stenosis in the cervical region has been confirmed by the increasing scientific interest in this area in recent years. International efforts such as the AO Spine RECODE-DCM initiative bring together researchers and healthcare professionals to establish research priorities and devise new approaches to patient care, particularly for individuals with cervical myelopathy symptoms [4–7]. Despite advancements in surgical techniques and diagnostic procedures, certain aspects of the mechanisms underlying neurological impairment in cervical spinal disorders remain unclear. A review of the literature was conducted using databases such as PubMed, Scopus, Google Scholar, and the Cochrane Library, covering the period from 2010 to 2024. The search terms included cervical spinal stenosis, cervical spondylotic myelopathy, and pathogenesis of cervical myelopathy. Priority was given to studies that focused on clinical/pre-clinical investigations and meta-analyses exploring pathophysiological processes and therapeutic innovations. The data were analyzed thematically.

This review covers aspects of the pathogenesis of cervical myelopathy, from the anatomical and biomechanical prerequisites for compression to the molecular and cellular mechanisms responsible for spinal cord injury. Special attention is given to the interaction between static and dynamic compressive forces, vascular disorders, inflammatory processes, apoptosis, and key molecular pathways (CX3CR1, MMP-9, FasL). This allows us to identify areas of current knowledge that require further investigation, as well as potential areas for future research.

AIM

To analyze and synthesize the existing knowledge on the pathogenesis of degenerative cervical myelopathy.

ANATOMICAL AND BIOMECHANICAL FEATURES OF THE CERVICAL SPINE

The human cervical spine has a high degree of mobility and a complex anatomical structure. This creates prerequisites for effective support and movement of the head, as well as the vulnerability of the spinal cord to compression. Normally, the diameter of the spinal canal in the cervical region is between 17 and 18 mm, while the diameter of the spinal cord at the cervical enlargement is approximately 10 mm [8, 9, 10]. Even a slight reduction in spinal canal diameter can significantly limit space for the spinal cord, and patients with a spinal canal diameter of less than 13 mm have an increased risk of myelopathy. Absolute stenosis, or critical narrowing, is defined as a spinal canal diameter of less than 10 mm [11, 12] or a 40 % reduction in the spinal canal [13]. Congenital or constitutional stenosis of the spinal canal has been identified as an important risk factor: when patients with a stenosis develop degenerative changes, myelopathy occurs more frequently [8]. Therefore, the initial anatomical reserve of space surrounding the spinal cord in the cervical region varies among individuals and is therefore limited, leading to varying degrees of susceptibility to compression.

In addition to the canal diameter, several other anatomical structures contribute to the function of the spine. These include the bony and cartilaginous components of the neck, such as the seven cervical vertebrae, intervertebral discs, facet joints, and uncovertebral joints. Together, these form a complex structure that provides both flexibility and support to the spine. With age and exposure to mechanical stress, these structures may undergo degenerative changes, including dehydration, loss of disc height, the formation of bone spurs (osteophytes), and hypertrophy of the facet joints [14, 15]. These changes can lead to a reduction in the size of the intervertebral space, which can cause increased pressure on the vertebral bodies, joints, and ligaments. This can result in the formation of more bone spurs and thickening of the ligaments, further narrowing the spinal canal [11, 16]. Over time, these structural changes can reduce the space available for the spinal cord, leading to chronic compression of both the anterior and posterior portions of the cord. Anterior osteophytes and disc protrusions may compress the spinal cord from the front, while a thickened *Ligamentum flavum* may also compress it from behind [11, 14, 17]. In addition, a static factor that can often exacerbate stenosis is the ossification of the posterior longitudinal ligament, which is pathological ossification of this ligament, leading to narrowing of the spinal canal [11, 18, 19].

Biomechanical characteristics of the cervical spine contribute to dynamic factors that may lead to spinal

cord injury. The cervical region has the largest range of movement among all spinal regions, including flexion, extension, lateral bending, and rotation, which results in periodic changes in the shape and size of the spinal canal. During neck flexion, the spinal cord lengthens and stretches, potentially coming into contact with ventral bone spurs or herniated discs. Conversely, during extension, the distance between laminae decreases, causing a “fold” of the thickened *Ligamentum flavum*, which increases dorsal compression [11, 19, 20]. These movements can lead to a “pincer” effect, in which the spinal cord becomes compressed between anterior and posterior structures. Furthermore, even when the spine is at rest, there is micromotion of the spinal cord, which oscillates slightly within the canal in sync with blood flow and respiratory movements. In a narrowed spinal canal, these factors can lead to repeated minor trauma to neural tissue due to tension, shear, and frictional forces [4]. In cases of cervical instability (spondylolisthesis or trauma), dynamic compression can be exacerbated by excessive vertebral movement, with displacement greater than 3.5 mm or an angular change greater than 11° between vertebrae on functional radiographs indicating instability that may aggravate spinal cord injuries [11]. Even with fixed spinal stenosis, movements, especially extreme flexion-extension, can provoke compression. During extension, additional canal narrowing occurs due to the displacement of structures. During flexion, the spinal cord is excessively stretched over bony-disc protrusions [11]. In addition to direct compression, repetitive microtrauma plays an important role. With each change in spinal axis, the spinal cord undergoes tension (longitudinal) and shear (vertical) forces that can damage axons and neurons [4]. The combination of mechanical factors forms the basis for chronic spinal cord injury. In contrast to acute injury, the traumatic effect extends over time and leads to a gradual impairment of sagittal balance and a range of secondary pathological processes [21, 22].

The anatomical and biomechanical characteristics of the cervical spine, such as its relatively narrow spinal canal, presence of large neural structures, and significant mobility, determine the combined static and dynamic effects on the spinal cord. These factors play a central role in the pathogenesis of spondylotic myelopathy, as well as creating prerequisites for chronic neural tissue damage.

PATHOGENESIS

Vascular disorders and chronic ischemia. Chronic spinal cord compression is accompanied by impaired blood flow. Normally, the cervical spinal cord receives blood supply from the anterior spinal artery, paired posterior spinal arteries, and radiculomedullary arteries that enter through the intervertebral foramina. However, with degenerative changes, there are pathological vascular alterations, including thickening, hyalinization, and narrowing of these vessels [17]. Additionally, venous outflow may be impaired due to compression of the venous

plexuses, leading to increased venous congestion and edema [9, 23]. These changes collectively reduce the perfusion pressure in the spinal cord. Animal model studies and post-mortem data support the role of ischemia in the development of myelopathy. For example, experiments on dogs have demonstrated that deformation and constriction of the terminal branches of the anterior spinal artery surrounding osteophytes in spondylosis can lead to reduced blood flow in corticospinal pathways [9]. A classic study by S.K. Karadimas et al. [17] demonstrated that chronic compression in animal models results in a decrease in capillary density within the spinal cord and a reduction in gray matter perfusion. This decrease in blood flow can lead to local tissue hypoxia, particularly in areas subjected to maximum compression. Ischemia, in turn, initiates a cascade of metabolic abnormalities: ionic balance becomes disrupted, and ATP production decreases, resulting in energy depletion of neurons and glial cells. One consequence of hypoxia is the release of excitatory neurotransmitters (glutamate) and an influx of calcium into neurons, leading to the phenomenon of excitotoxicity, a process in which neurons die due to excessive stimulation and an imbalance of ions [11, 24–26]. Therefore, chronic insufficient blood supply aggravates direct mechanical damage by expanding the area of spinal cord injury through metabolic and biochemical effects.

It is important to acknowledge that the role of chronic ischemia in cervical myelopathy is still not fully understood. Several experimental and clinical studies have failed to identify clear signs of ischemic damage with moderate spinal stenosis [9]. While pathological changes associated with ischemia can be clearly detected in severe cases of compression, in cases with less severe compression, the spinal cord can still receive sufficient blood supply via collateral vessels [9]. Moreover, many animal models of cervical myelopathy have reproduced acute or subacute compression, which may not fully reflect the chronic nature of the condition in humans [4]. However, the available evidence suggests that chronic hypoperfusion of the spinal cord plays a significant role in the pathogenesis, particularly in later stages of the disease, exacerbating damage to neurons and glial cells.

Blood-spinal cord barrier dysfunction. One of the main consequences of prolonged mechanical injury and ischemia is the disruption of the integrity of the blood-brain barrier at the level of the spinal cord, also known as the blood-spinal cord barrier (BSCB). Under normal conditions, the vascular system of the spinal cord exhibits selective permeability, with capillary endothelial cells connected by tight junctions and surrounded by a basement membrane consisting of *laminin*, *collagen IV*, *nidogen*, and *heparan sulfate proteoglycans*, as well as astrocytic foot processes, and supported by pericytes [18, 27, 28]. This structure, known as the neurovascular unit, protects neural tissue by preventing the uncontrolled entry of substances and cells from the bloodstream. With chronic compression, damage to the microvascular system occurs, as indicated by the reduction in the number of intact capillaries,

loss of endothelial cells, and disruption of laminin within the vessel walls [18]. Morphologically, this suggests degradation of the basal lamina and disruption of tight junctions, leading to an increase in BSCB (blood-spinal cord barrier) permeability. Indeed, experimental studies have shown that progressive stenosis in cervical myelopathy is accompanied by disruption of the barrier and entry of large molecules and blood cells into the spinal cord parenchyma [29, 30]. Fragmentation of the endothelial lining and basal lamina facilitates plasma extravasation, leading to vasogenic edema manifested as microvacuolation of neural tissue [18, 23]. At the same time, conditions are created for immune cell migration, as the spinal cord normally functions as an immunologically privileged organ, isolated from cells of the peripheral immune system. However, with barrier disruption, leukocytes, such as neutrophils and monocytes, can infiltrate the affected area. Under inflammatory conditions, the vascular basal lamina can also be split into layers, creating "pseudogaps" through which leukocytes can migrate [18].

The molecular mechanisms of BSCB (blood-spinal cord barrier) damage in degenerative myelopathy are linked to the action of proteolytic enzymes and inflammatory mediators. Research has shown that the activity of matrix metalloproteinases (MMPs), particularly MMP-9, is elevated in the spinal cord of patients with cervical myelopathy. MMP-9 is an enzyme produced by neutrophils and endothelial cells that degrades extracellular matrix components, including collagen and laminin in the basement membrane. This process contributes to increased vascular wall permeability. Elevated levels of MMP-9 have been detected both in the spinal cords of patients with cervical myelopathy and in animal models. In addition to MMP-9, other factors that contribute to increased permeability in foci of chronic compression include MMP-2, urokinase plasminogen activator (uPA), cytokines such as interleukin-1 β , -6, -8, FasL, and TNF- α . These substances can weaken the endothelial cell connections. Initially, these mediators were studied in the context of acute spinal cord injury, which causes temporary (for several weeks) disruption of the blood-spinal cord barrier (BSCB), followed by recovery [18]. However, in the case of chronic spinal cord compression, the effect of these mediators is more long-lasting, resulting in persistent "leakage" of the barrier. As a result of the disruption of the BSCB, a specific microenvironment is created within the spinal cord tissue that promotes chronic inflammation and edema, exacerbating neuronal damage.

The inflammatory cascade and the role of microglia. One of the most significant differences in the pathogenesis of chronic cervical myelopathy compared to acute traumatic injury lies in the prolonged inflammatory response that occurs in chronic compression. Under conditions of continuous mechanical trauma and intermittent ischemia to the spinal cord, a chronic neuroinflammatory response develops. The inflammatory process in myelopathy consists of two components: an initial reaction directly triggered by the mechanical compression of neural

tissues, and a secondary response sustained by chronic ischemia and disruption of the blood-spinal cord barrier [4, 17, 26]. The mechanical stretching and deformation of the spinal cord activate the immune response within the central nervous system, leading to the activation of microglia, which are resident macrophage-like cells of the central nervous system (CNS). Already at the early stages of compression, microglial and astrocytic cells respond to stress, with hypertrophy and changes in their phenotype occurring. Experimental models have demonstrated a significant accumulation of activated microglia/macrophages at the site of inflammation. Additionally, increased neutrophil activity has been observed at the level of injury after 6 weeks. Nevertheless, the primary role belongs to microglia and monocyte-derived macrophages, which are dominant in both the early and late stages of compression [17]. Consequently, a cycle of events is created: mechanical damage and ischemia attract inflammatory cells, which in turn release substances that exacerbate tissue damage and disrupt the vascular barrier.

It is important to note that the regulation of neuroinflammation in cervical myelopathy depends on signaling through the CX3CL1-CX3CR1 pathway. Fractalkine (CX3CL1), a chemokine produced by neurons, exists in both membrane-bound and soluble forms. Its receptor, CX3CR1, is highly expressed on microglia. Under normal conditions, neuron-microglia interactions through fractalkine play a role in maintaining immune homeostasis in the CNS, preventing excessive microglial activation. However, under conditions of ischemia or trauma, this mechanism is disrupted. Ischemia leads to microglial activation through the CX3CL1/CX3CR1 signaling pathway, leading to an inflammatory response. In the context of chronic compression, mice lacking the CX3CR1 receptor have an attenuated microglial response. Their spinal cords exhibit lower levels of activated microglia and macrophages, as well as reduced production of pro-inflammatory cytokines such as G-CSF, M-CSF, and CXCL10, compared to control animals under similar conditions. These data suggest that the aforementioned pathway is a crucial mechanism linking chronic hypoxia/ischemia with neuroinflammation in cervical myelopathy, and that microglial activation significantly contributes to the progression of injury [17, 31].

Activated microglia and macrophages release a variety of inflammatory mediators, which exacerbate neuronal damage in the spinal cord. Increased levels of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) and chemokines (IL-8/CXCL8, MCP-1), as well as the activation of pro-inflammatory transcription factors such as NF- κ B, have been detected in the tissue of the spinal cord in myelopathy [25, 32]. These cytokines increase vascular permeability and cause edema, as well as exert direct toxic effects on neurons. Additionally, under conditions of chronic inflammation, astrogliosis occurs in the spinal cord, where astrocyte proliferation occurs around the site of injury as a response to prolonged inflammation. This can lead to the formation

of a glial scar, which impedes axon regeneration [33, 34]. Interestingly, the observed changes in the degeneration process are similar to those seen in acute traumatic spinal cord injury. Both involve endothelial dysfunction, the infiltration of macrophages and microglia, as well as the release of cytokines, ultimately leading to cell death [18, 21]. However, in the case of degenerative disorders, these processes occur more slowly and chronically. This, on the one hand, allows for some compensation and partial functional recovery between episodes of exacerbation. On the other hand, it also leads to cumulative damage over an extended period of time.

Apoptosis and neuronal degeneration. The end-point of the pathological cascade in cervical myelopathy is the irreversible death of spinal cord cells, including neurons and oligodendrocytes that provide the myelin sheath for axons. Chronic compression causes apoptosis, or programmed cell death, in neural tissue that can persist long after the onset of the disease. Experiments have shown that even 10 weeks after chronic compression is modeled, numerous cells undergoing apoptosis, including anterior horn neurons and oligodendrocytes, continue to be present in the spinal cord [18]. Interestingly, apoptosis occurs not only in the compression area but also in distant areas of the spinal cord, above and below the site of compression, indicating secondary damage via Wallerian degeneration of descending and ascending pathways [14]. Oligodendrocyte death results in loss of myelin on axons, while neuronal loss leads to atrophy of gray matter. Both processes have been morphologically confirmed: at autopsy, patients showed foci of white matter demyelination and loss of gray matter neurons [14, 35]. Apoptosis, a “programmed” form of cell death, is triggered by specific molecular pathways that are activated during chronic injury.

Studies have identified several key apoptosis-promoting signaling mechanisms involved in degenerative myelopathy. One such mechanism is the activation of the Fas (CD95) receptor and its ligand, FasL. This pathway, which traditionally triggers apoptosis in immune cells, is also involved in neuronal and oligodendrocytic death in central nervous system (CNS) pathology. Increased expression of FasL has been observed in microglial and other cells in spinal cord tissue in individuals with cervical myelopathy, and this correlates with neuronal apoptosis [24]. Animal and human post-mortem studies have shown that blocking FasL reduces the levels of apoptosis in neurons and oligodendrocytes, leading to improved functional outcomes. In other words, the FasL-mediated pathway plays a major role in the “execution” of cells during chronic compression, and blocking it has a neuroprotective effect [24].

Another important pathway of apoptosis in cervical myelopathy involves the inflammatory cascade mediated by cytokines. Tumor necrosis factor- α (TNF- α), released by activated immune cells, triggers neuronal apoptosis by activating specific receptors on the neurons. Additionally, TNF- α enhances local inflammation, creating an environment that is lethal to cells. Mitogen-activated protein

kinases (MAPKs), such as JNK and p38 kinases, are also involved in this process. Activation of these kinases has been observed under conditions of chronic compression, leading to a series of intracellular events that culminate in cell death [18]. The role of NF- κ B, a transcription factor that can activate programmed cell death under chronic stress, has also been recognized. Furthermore, pro-apoptotic and pro-inflammatory mechanisms appear to be closely linked. For instance, TNF- α is both a cytokine and inducer of apoptosis. NF- κ B activation, in turn, can both maintain inflammation and promote apoptosis. In a mouse model of myelopathy in genetically predisposed animals, it has been shown that blocking the TNF- α signaling pathway reduces oligodendrocyte death [27, 36], confirming its role in the process. Thus, chronic inflammation and apoptosis in degenerative cervical myelopathy forms an interconnected cascade that leads to neurodegeneration – a gradual loss of neural elements in the spinal cord. Macroscopically and microscopically, this is manifested as the development of cystic-vacuolar lesions in the spinal cord, gliosis, demyelination of long tracts, and atrophy of neural tissue [18, 35]. Clinically, neurodegeneration corresponds to an irreversible functional deficit – even after decompression, persistent neurological impairment persists.

In summary, it is important to emphasize that the pathogenesis of cervical degenerative myelopathy is a multifactorial and cyclic process. Static and dynamic mechanical forces initiate a series of changes in the vascular, barrier, inflammatory, and molecular levels, which collectively lead to the gradual death of spinal cord cells. These processes are interconnected: compression causes ischemia and disruption of the blood-spinal cord barrier; ischemia and barrier disruption lead to inflammation; inflammation triggers apoptosis; and apoptosis and neural tissue damage further exacerbate inflammation (through the release of antigens and breakdown products that attract additional immune cells). This creates a vicious cycle of chronic injury in the affected spinal cord. Ongoing research continues to uncover new aspects of this complex process, including genetic factors and systemic factors such as metabolic and immune features of the individual.

ROLE OF HEREDITY IN THE DEVELOPMENT OF DEGENERATIVE CERVICAL SPINAL STENOSIS

The role of the *NAT1* and *NAT2* genes in spinal tissue aging is currently under investigation, which may lead to the development of degenerative changes and spinal cord compression [37]. Several studies have demonstrated the importance of acetylation processes in the pathogenesis of degenerative-dystrophic spinal conditions, such as stenosis of the spinal canal and ossification of the *Ligamentum flavum*. It has been established that the expression of acetyltransferase genes, such as *NAT1*, *NAT2*, *AANAT*, and *NAA20*, in *Ligamentum flavum* tissue is correlated with the development of pathological changes. A “slow” acetylation phenotype has been observed

more frequently in patients with ossification, and polymorphisms in the *NAT1* and *NAT2* genes are associated with an increased risk of ectopic bone formation. Women appear to be more prone to *Ligamentum flavum* ossification, which may be related to differences in estrogen receptor gene expression (*ESR1* and *ESR2*). The identified gene expression patterns suggest that acetyltransferases may be potential biomarkers for predicting the risk of complications and guiding personalized approaches to preventing epidural fibrosis and stenosis. Expression of the *NAT1* and *NAT2* genes in ligaments indicates their involvement in regulating connective tissue metabolism, and polymorphisms of these genes may be a marker for individual susceptibility to pathology. Gender differences and the association between “slow” acetylation and the risk of ectopic ossification highlight the importance of considering genetic factors in surgical planning. These findings open up possibilities for developing pharmacological agents that modulate acetylation and may reduce the incidence of postoperative complications. Further research should focus on investigating the effect of acetyltransferase inhibitors and activators on connective tissue remodeling processes in experimental and clinical settings [37, 38, 39].

DISCUSSION

In recent decades, there has been a significant accumulation of knowledge regarding the key factors in the pathogenesis of cervical spinal stenosis, particularly cervical myelopathy. A combination of static and dynamic factors affecting the cervical spine has been identified as leading to chronic spinal cord injury, triggering a cascade similar to that seen in chronic brain or spinal cord trauma. This includes local ischemia, edema, immune cell infiltration due to disruption of the vascular barrier, persistent neuroinflammation with activation of microglia, cytokine release, involvement of molecules such as CX3CR1, MMP-9, FasL, and TNF- α , and subsequent apoptosis of neurons and oligodendrocytes, resulting in spinal cord degeneration, including demyelination, atrophy, and permanent neurological deficits.

Despite significant advances in our understanding of the pathogenesis of cervical myelopathy, there are still several important questions that remain unanswered. For example, it is unclear why some patients with the same degree of stenosis develop severe symptoms while others experience minimal symptoms [17, 40]. It is likely that individual factors, such as age, genetic variations, concomitant conditions, and differences in the immune system, play a role in determining a person's susceptibility to myelopathy. Protective mechanisms such as autoregulation of blood flow, antioxidant capacity, and functional reserve of the spinal cord may also contribute to the development of myelopathy. Further research into these areas is needed to gain a better understanding of the risks associated with cervical myelopathy and develop more personalized treatments.

Second, the precise molecular mechanisms through which neurodegenerative processes occur in chronic compression are not fully understood. Researchers continue to investigate the role of specific cytokines and receptors. Can blocking TNF- α or other mediators slow the progression of myelopathy significantly? What role do autoimmune components play? Is the production of autoantibodies during prolonged spinal cord injury able to exacerbate the process? Gene expression and proteomic studies in degenerative cervical myelopathy have revealed changes in multiple mechanisms associated with inflammation, apoptosis, and remyelination. These findings provide a basis for developing new therapeutic strategies. Anti-inflammatory and neuroprotective agents that can modulate microglial activity or protect oligodendrocytes from death are being developed. Experimental examples include the use of specific neuromodulators, which have led to reduced Fas-mediated apoptosis and improved outcomes in animal models [41]. In terms of clinical relevance, the key question is whether medication, such as anti-inflammatory or vasodilator agents, can slow the progression of myelopathy or enhance recovery after surgical decompression. While surgery continues to be the primary treatment for spondylotic myelopathy, combining surgical interventions with adjunctive therapies that target molecular pathways involved in the pathogenesis of the condition presents a promising avenue for research.

Third, further research is needed into repair processes. It has been established that following surgical decompression, not all patients experience complete recovery, with neurological deficits often remaining, particularly if myelopathy existed for a prolonged period prior to surgery. Why is regeneration limited? Attention is once again drawn to astrogliosis and irreversible damage, as the glial scar may hinder axon growth and lost neurons do not regenerate. Ongoing research in regenerative medicine seeks to identify ways to stimulate repair mechanisms, ranging from the transplantation of stem cells and oligodendrocyte progenitors to the application of growth factors. Before such approaches become a reality, however, it is essential to clearly comprehend the barriers to regeneration in chronic spinal cord injuries. Perhaps one significant factor is prolonged inflammation, whose modulation could enhance the environment for recovery.

CONCLUSION

The pathogenesis of degenerative cervical myelopathy is a complex interaction of biomechanical and biological factors. Chronic compression of the spinal cord triggers a cascade of events, including local vascular disorders and systemic neuroinflammation, leading to the gradual death of neurons and functional loss. To date, the condition has been actively studied, with recent literature providing deeper insights into the molecular mechanisms and processes involved in spinal cord compression. However, significant gaps in our understanding

of the development of the pathology remain, necessitating further research. Priority areas for future research include understanding the causes of variability in myelopathy progression among patients, developing strategies to protect neurons, and creating more accurate models that replicate chronic compression in humans. In the future, the integration of knowledge regarding pathogenesis with clinical data has the potential to lead to novel therapeutic strategies that may slow or prevent the progression of neurological degeneration in cervical myelopathy, thereby improving treatment outcomes for affected individuals.

Conflicts of interest

The authors declare no conflicts of interest.

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