Review paper

Degenerative cervical spine disease: pathogenesis and symptoms

Choroba zwyrodnieniowa odcinka szyjnego kręgosłupa – patogeneza i objawy

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Abstract

Cervical discopathy is a degenerative process in the intervertebral disc and the structure of the fibrous ring. Due to the processes of proteoglycan breakdown and collagen structure, the nucleus pulposus is dehydrated and susceptible to the damaging process. The stretching of the ring leads to its tearing and the appearance of a hernia of the nucleus pulposus. These changes lead to the growth of degeneration in the anatomical structures, i.e. the yellow ligament or intervertebral joints. Treatment of the disease should take into account the mechanism of degeneration and biomechanics of the cervical spine.

Streszczenie

Dyskopatia szyjna to przewlekły proces degeneracyjny zachodzący w obrębie krążka międzykręgowego, jak również w strukturze samego pierścienia włóknistego. Wskutek wielu złożonych procesów rozpadu proteoglikanów oraz struktury kolagenu dochodzi do procesu dehydratacji jądra miażdżystego oraz większej podatności na procesy uszkadzające. Rozciąganie pierścienia włóknistego powoduje jego przedarcie i pojawienie się przepukliny jądra miażdżystego. Zmiany te prowadzą do narastania procesów degeneracyjnych w anatomicznych strukturach sąsiednich, takich jak więzadło żółte czy stawy międzykręgowe. Rozwój choroby zwyrodnieniowej jest powolny, jednak niektóre czynniki mogą znacznie przyspieszyć rozwój schorzenia. Leczenie powinno uwzględniać mechanizm powstawania zwyrodnień oraz biomechanikę odcinka szyjnego kręgosłupa.

Introduction

Degenerative cervical spine disease is a degenerative process of a chronic nature. It covers the intervertebral disc and the anatomical structures of the adjacent motor segment. As a consequence of the natural processes taking place in the aging spine and the pathological processes of the disc, secondary changes occur in the vertebral bodies and the ligament complex, i.e. overgrowth of the ligament, intervertebral degeneration or formation of osteophytes [1]. The development of degenerative disease is slow, but some factors may accelerate the development of the disease significantly.

Pathophysiology of the degenerative process

The development of degenerative disease from one-level discopathy to spondylosis proceeds in several stages. Within the matrix of the nucleus pulposus, a cascade of biochemical processes takes place that initiate a number of changes in the anatomical structures of the spinal movement segment.

Processes at the level of proteoglycans and the collagen structure of the nucleus pulposus begin early. The ratio of keratin sulfate to chondroitin sulfate increases, which results in dehydration of the intervertebral disc. Degenerative changes also occur in the structure of the fibrous ring. The decrease in elasticity and the loss of load carrying capacity by the nucleus causes stretching of the rings and then their tears. As a result, the disc is accentuated and a hernia of the nucleus pulposus is formed. The disc herniation is often the first stage in the development of degenerative cervical spine disease. However, research suggests that the immunohistochemical and histological changes of the hernia itself may differ from the changes occurring in the "aging" nucleus pulposus in the course of degenerative cervical segment [2].

In degeneration of the disc, processes begin in the structure of the nucleus. At the biochemical level, the concentration of some proinflammatory cytokines increases. The levels of interleukin-1, tumor necrosis factor α (TNF-α), and nitric oxide synthase increase, while the level of tissue metalloproteinase inhibitor (TIMP) decreases. Under the conditions of the TIMP standard, it acts suppressively on metalloproteinases of the nuclear matrix produced by chondrocytes. Therefore, correct TIMP levels provide control over the degenerative processes of the intervertebral disk structure. In the case of "aging" processes, the disc, as a result of the drop in the TIMP level, accelerates the degenerative processes. As a result of the macrophage activity and secretion of the hyperoxide, proteoglycans and hyaluronic acid are degraded [3] (Figure 1).

The etiology of degenerative disc and spine disease is multifactorial. Some changes of the intervertebral disc proceed with age. As the years go by, the cellularity of the nucleus pulposus and its ring decreases. The concentration of proteoglycans drops and due to the increase in the amount of collagen type 1, the disc becomes more fibrous. As a result of these changes, it is more susceptible to injuries and can be easily torn [3].

Recently, a lot of research has been devoted to genetic factors. They are considered to be an important factor in the development of spondylosis of the spine and degeneration of the intervertebral disc. T-allele Taq I- vitamin D receptor (and receptor gene polymorphism) may contribute to the development of the disease. Research suggests that it also plays roles in the case of hernia in people before the age of 40 [4]. The COL9A2 gene is involved in the production of collagen. Studies have reported that a tryptophan encoded by a gene in one of the collagen IX polypeptide chains may lead to loss of stability and increase susceptibility to damaging factors. Gene studies that control collagen synthesis are currently underway. The scientists are looking for deviations in the connective tissue structure that may play a role in the resistance of the nucleus to environmental factors (genes: COL1A1 Sp1-collagen I, COL9A3 Trp3-collagen IX, COL11A2-collagen XI) [5].

The studies focus on the structure of the matrix of the nucleus pulposus. Aggrecan is one of the proteoglycans responsible for the proper hydration of the disc. It also participates in the formation of chondroitin sulfate structure. Currently, for the aggrecan gene, the polymorphism of a variable number of tandem repeats in the genome (VNTR) is analyzed. The correct number of repeats in the chondroitin sulfate encoding gene is between 13 and 33 nucleotides. The results of the study show that a smaller number of sequence repetitions may contribute to the growth of multilevel discopathy development [1]. The number that appears to be the limit (norm) of nucleotide repeats is 25–26 repetitions. Patients with "short" alleles (number of repeats 13–26) were more likely to develop discopathy faster [6].

The processes of apoptosis and their control are very important in the process of damage to the intervertebral disc matrix. In the case of a degenerative disk

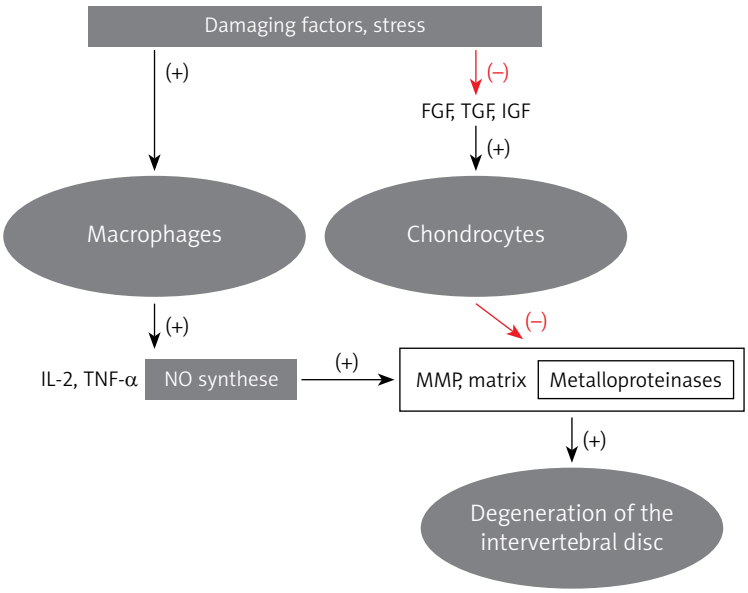

Figure 1. Cytokines acting on cells inside the nucleus pulposus

IL-2 – interleukin 2, TNF-α – tumor necrosis factor α, FGF – fibroblast growth factor, TGF – transforming growth factor, IGF – insulin-like growth factor.

and a healthy disc, the enzymes that monitor the correct course of the process show different levels (caspase-9). CASP 9 gene polymorphism, GG genotype increases the risk of the disease 2.5 times in relation to the AA genotype. DR 4 and DR5 receptors are involved in the control of apoptosis. They bind the TRAIL ligand (TNF dependent apoptosis-inducing ligand). Overexpression of receptors in the case of genetically determined factors leads to acceleration of programmed mechanisms of cell death and increases the incidence of degenerative disease of the intervertebral disc [7].

Most current studies are based on the analysis of lumbar discopathy. However, existing genetic mechanisms seem to play a similar role in cervical discopathy. It should be taken into account that the combination of genetic factors, micro-injuries and environmental factors probably leads to the progression of the disease.

Mechanical strains of the cervical spine play a key role in the degeneration process. Repetitive micro-injuries or extreme injuries (rugby players) lead to damage to the structure of the nucleus pulposus (accelerated breakdown of collagen and proteoglycans) and the fibrous ring. Lack of activity weakens the strength of the cervical muscles. Similarly, considerably important in the development of the disease are abnormal habits disturbing the spine setting in the cervical lordosis or setting the head in a forced position with the shift of the center of gravity towards the front. Discopathy proceeds in stages that follow a specific sequence. In the first stage, mechanical factors cause stretching of the fibrosus ring. Then, within the ring lamellas, there are progressive tears, which results in a hernia of the nucleus pulposus in the third stage. As a result of the damage of the nucleus pulposus and the fibrous ring, the height of the intervertebral disk decreases. There is a natural difference in height between the surface at the front and posterior ligaments. As a consequence, the center of gravity of the head moves forward. This stimulates the processes of osteophyte production, overgrowth of the yellow ligament and degeneration in intervertebral joints and Luschka's joints. Transferring loads from the anterior column to the intervertebral joints leads to hypertrophy of the intervertebral joints. The process results in narrowing of the spinal canal and reduction of the spinal cord's fluid reserve, which may lead to the development of cervical myelopathy [8].

Symptoms

There are three main symptoms of cervical discopathy, i.e. axial cervical spine pain, root aches and cervical myelopathy. It is estimated that degenerative changes in the cervical spine affect 12% of the female population and as many as 17% of men aged 20 years. However, most cervical discopathy remains asymptomatic. Significant compression of the spinal cord in the cervical spine, which may be the basis for the development of cervical myelopathy, is observed in 7.6% of patients over 50 years of age. Over the age of 60, cervical discopathy can affect more than 85% of the population [9].

There is a tendency of degeneration occurring in younger patients and an increase in the number of symptomatic patients. Clinical symptoms of cervical discopathy usually appear in patients between 40 and 60 years old. It should be noted that statistically the disease affects men more often than women. The incidence ratio of women to men is approximately 2 : 3 [10].

Degenerative diseases of the cervical spine usually relate to the level of C6/C7 (up to 69% of discopathy with herniation of the nucleus pulposus), then the level of C5/C6. Neck pain is the first symptom of cervical discopathy and is the second symptom of spinal discopathy after pain in the lumbar region. Modic modifications have been divided into three types; they concern end plates and subchondral parts of adjacent structures. In stage 1, there are gaps in the border plaque and granulation tissue. As a result, marrow edema occurs. Grade 2 means breakage of the end plates and fatty degeneration of parts of the vertebral body adhering to the disc. In contrast, grade 3 is ossification of the bone marrow. Symptoms of Modic type 1 are considered to be symptomatic, involved in the mechanism of axial pain development of the spine. Studies shows that the changes in end plates are caused by "infiltration" of plaques with immunoreactive cells and the production of tumor necrosis factor (TNF) [11].

The mechanism of neck pain is complex. Biochemical changes in the muscles of the neck and the reaction of the intervertebral joint to the damaging factor (free nerve endings and substance P) can participate in it. As a result of stimulation by inflammatory interleukins, i.e. IL-1, IL-2, IL-4, IL-6, IL-17, IL-20, there is increased expression of nerve growth factor (NGF) mRNA. The consequence of the cascade of NGF synthesis processes is the increase in the number of free nerve endings within 1/3 of the external part of the fibrous ring. According to current research, this is the sequence of formation and one of the mechanisms of discogenic pain [12] (Figure 2).

The root symptoms result from the compression of nerve structures by the hernia of the nucleus pulposus or the foraminal stenosis. The hernia appears most often at C6/7 (69%) and C5/6 (19%), and the symptoms are due to the nerve compression of the seventh and sixth respectively at the C5/6 level. The root symptoms depend on the level of the hernia of the nucleus pulposus. Patients may report shoulder pain and sensory abnormalities that radiate to the arm (C5 root), forearm and fingers (finger I-root C6, fingers II and III-C7, IV and V-C8). Defective symptoms in the form of paresis due to root compression may affect the

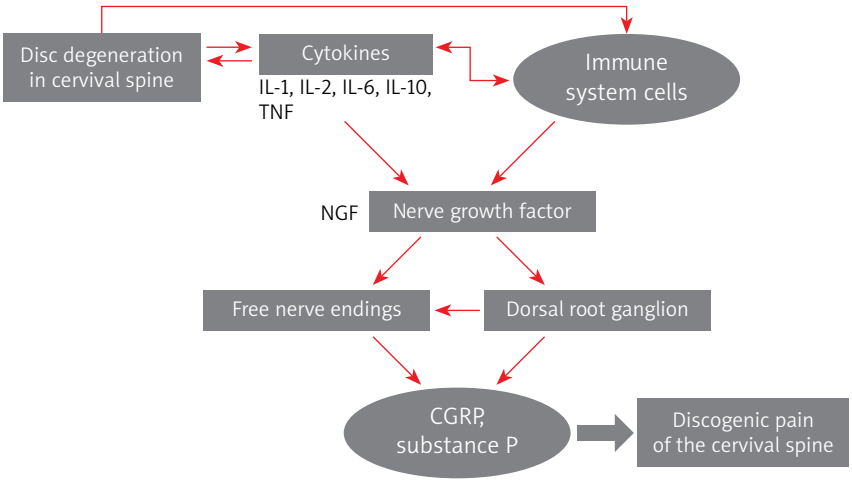

Figure 2. Diagram of the formation of discogenic neck pain

IL – interleukin, TNF – tumor necrosis factor, NGF – nerve growth factor, CGRP – derived peptide of the calcitonin gene.

deltoid muscle, arm muscles, flexors and extensors of the forearm as well as the small muscles of the hand. Depending on the location, the reflexes of the deltoid muscle (C5 root), biceps muscle (C6 root) and the triceps arm (C7) are weakened. Compression of the C4 nerve root may provoke axial cervical pain, while the left C6 root is referred to as a "pseudoangina", as it may imitate aches similar to coronary syndrome. In the case of hernias with C8 nerve root compression, the Horner syndrome may develop [13].

During the examination, the patient may also have a positive Spurling symptom (the applied force on the top of the head by the examiner intensifies the symptoms). The shoulder test is not particularly sensitive, while the arm lift reduces the root discomfort (positive test). Lhermitte's sign is rarely positive, but it can also occur in cervical radiculopathy and myelopathy.

The mechanism of pain in the nature of cervical radiculopathy begins with the mechanical pressure of the dorsal root ganglion (increase in the concentration of substance P) and irritation of the nerve root itself. There is a decrease in blood circulation, which stimulates the production of inflammatory agents. The amount of TNF-α and other mediators increases. A similar process takes place within the intervertebral disc. Excessive production of inflammatory mediators is responsible for root pain [14].

Other clinical symptoms are present in myelopathy (CSM). CSM is the most common cause of limb paresis without connection to trauma. It should be emphasized that in 26.3% of patients with non-traumatic cervical myelopathy, advanced cervical discopathy and spondylosis were considered to be a cause [15].

Symptoms of myelopathy develop slowly. Walking instability, increased tension and discrete paresis of the lower limbs (especially proximal) are early symptoms of CSM. In the initial period of the disease, the triceps muscle and small muscles of the hand are weakened. This leads to difficulties in writing and performing precise tasks, such as buttoning, or capturing small objects with fingers. Sensory disturbances can affect the whole hand. In the lower extremities the sense of vibration is weakened. There are pathological reflexes, i.e. the symptom of Hoffman or Babinski. Bladder control disorders in the form of an urgent urge rarely take the form of urinary incontinence. The group of symptoms most commonly occurring in the course of myelopathy is the so-called transverse core injury syndrome. Symptoms may be acute, especially after an injury. When the central spinal cord syndrome appears, the severity of the paresis in the upper limbs is greater than in the lower ones. Rare forms of symptoms of myelopathy are a syndrome similar to amyotrophic lateral sclerosis (damage to the "upper motor neuron" in the lower limbs and "lower motor neuron" in the upper limbs) or Brown-Sequard syndrome [16].

The development of myelopathy is influenced by static factors related to anatomy and progressive spinal canal stenosis (degeneration of the intervertebral disc, ossification of the posterior longitudinal and yellow ligaments, congenital "narrow spinal canal"). Dynamic factors in the form of straightening and bending movements of the core at the level of compression are the second element of the CSM cascade. These changes lead to impaired blood supply, oligodendrocyte apoptosis and a local inflammatory response [17]. The mechanisms of glutamate transformations in CSM are also examined as a disease similar to neurodegenerative syndromes. It has been observed that in the case of myelopathy, the decreased expression of calcium binding proteins and AMU GluR2 receptors makes neurons sensitive to damage [18].

Treatment

In the case of discopathy, the method of choice is anterior cervical discectomy with fusion (ACDF). This method is intended for hernias at C3-C7 levels. It can be performed on one or more levels and the implant can be additionally fastened with screws or a front plate. When stabilizing above two levels, it is recommended to use the front plate. For bone union after surgery, a cervical collar (Philadelphia or soft type) is routinely used for 4–6 weeks. Some studies, however, question the need to use a collar after ACDF [19]. Proper selection of the height and shape of the implant allows correction of the disturbed sagittal balance and thus influences the result of the treatment.

In advanced cervical spondylosis with spinal stenosis from the frontal access a corpectomy is performed. The removed shaft is replaced with a prosthesis and it is supplemented with bone grafts and stabilized with a plate. The oblique corpectomy treatment allows the stability of the spine.

To maintain segment mobility, a removable cervical disc prosthesis is implanted from the anterior access. It is an alternative method for the effective treatment of neck pain and shoulder pain.

An optional access to the spinal canal stenosis is the posterior laminectomy. It allows decompression of the cervical spinal cord and is indicated for the pathology of the posterior spinal canal, i.e. ossification of the posterior longitudinal ligament and multilevel or myelopathic lesions. However, it can also initiate a cervical dislocation of the cervical segment, lead to shifting the center of gravity of the head forward and activate the mechanism of progressive deformation. The use of screws allows for better correction of the C2-C7 lordosis angle and may prevent progressive deformation of the cervical spine [20].

The posterior access can also be used for cervical foraminotomy. This method allows removal of lateral extrusion of the spinal canal or decompression of the stenosis, while maintaining the stability of the spine. It does not require the use of implants [21].

Laminoplasty is an alternative to laminectomy. This technique is used to treat spinal stenosis and cervical myelopathy. It allows one to maintain the mobility of the section, prevents the formation of scars on the dural sac and ensures decompression of the cervical cord [22].

Physiotherapy plays an important role in the prevention of development of spinal discopathy. It is important both in the prevention and the treatment itself. There are many effective methods of fighting pain and preventing mechanical overloading of individual sections of the spine.

One of them is MDT. McKenzie therapy is one of the better documented methods of pain management in the course of spinal discopathy in EBM. It includes 5 principles: examination (assessment), classification, treatment with repeated movements, muscle strength improvement, and education with changing habits (prevention). Identifying changes in the location of pain on the basis of mechanical evaluation allows for the improvement of the treatment outcome [23].

Cyriax therapy and orthopedic manual therapy (OMT) are also tools in treating discogenic back pain. Deep riverside massage with traction and manipulations are used as effective therapeutic procedures [24].

Summary

Cervical discopathy is already classified as a civilization disease. Due to its complex mechanism of formation, it still requires further research. Understanding the molecular and genetic factors of progressive degenerative changes and biomechanics of the cervical spine may allow effective treatment of this disease in the future.

Conflict of interest

The authors declare no conflict of interest.

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