CERVICAL SPONDYLOMYELOPATHY (WOBBLER SYNDROME) UPDATE ON PATHOGENESIS

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Cervical spondylomyelopathy (CSM) or wobbler syndrome is arguably the most common disease of the cervical spine of large and giant breed dogs. Data from the Veterinary Medical Database indicates a prevalence of CSM in Doberman Pinschers of 5.5%, and 4.2% in Great Danes (which may be an underestimate of its prevalence). In most reports, these two breeds account for 60-70% of the cases. CSM is also a controversial disease. A variety of names (at least 15) have been used to describe the disease, cervical vertebral instability, cervical malformation/malarticulation syndrome, and disc-associated wobbler syndrome, are some of the terms most commonly used. The critical issue for such inconsistency is essentially a poor understanding of the causes and pathogenesis of the disease. The disease is basically characterized by compression of the spinal cord and/or nerve roots which then leads to neurological deficits and neck pain. However, Dobermans and Great Danes can have spinal cord compression without signs of cervical spondylomyelopathy, highlighting the complex nature of the disease.

The etiology of CSM is not totally understood but there is evidence of a congenital and genetic etiology. A recent study found that CSM in Dobermans is inherited with an autosomal dominant mode of inheritance with incomplete penetrance.

PATHOPHYSIOLOGY

- The pathophysiology of CSM involves both static and dynamic factors. The key static factor is vertebral canal stenosis. It may be an absolute vertebral canal stenosis (which then causes direct spinal cord compression and neurological signs) or a relative vertebral stenosis, which by itself does not lead to myelopathic signs, but predisposes the patient to develop myelopathy. Despite some degree of overlap, the pathophysiology of the spinal cord compressions can be divided into osseous or disc-associated compression.
- Disc-associated compression is typically seen in middle-aged large breed dogs (mostly Dobermans). It is caused by a combination of intervertebral protrusion with or without ligament hypertrophy (either the dorsal longitudinal ligament or ligamentum flavum).
- Three factors act in combination to explain the pathophysiology of disc-associated CSM: a) relative vertebral canal stenosis, b) more pronounced torsion in the caudal cervical spine leading to intervertebral disc degeneration, and c) protrusion of larger volume discs in the caudal cervical spine. Affected dogs are apparently born with a congenital vertebral canal stenosis. The vertebral canal stenosis per se does not lead to clinical signs, but predisposes them to the development of clinical signs. The vast majority of the disc-associated spinal cord compressions are located in the caudal cervical spine, affecting the discs C5-6 and C6-7.
- The pathophysiology of osseous or bony associated CSM is different. Osseous associated CSM is seen predominantly in young adult giant breed dogs. Even though a hereditary basis is unproven, a familial predisposition has been identified. Giant breeds usually have severe absolute vertebral canal stenosis secondary to proliferation of the vertebral arch (dorsally), articular facets (dorso-laterally) or articular facets and pedicles (laterally). The cause of the compression appears to be a combination of vertebral malformation and osteoarthritic/osteoarthrotic changes at the level of the articular facets. Even though most giant breed dogs have osseous compression, occasionally these compressions are complicated by disc protrusion, especially in older dogs. Ligamentous compression (ligamentum flavum) may be associated in the pathophysiology of the disease in giant and

large breed dogs, but pure ligamentous compression as the single source of compression appears uncommon.

- Critical to the development of clinical signs in CSM-affected large breed dogs is the concept of dynamic lesions. Dynamic spinal cord compressions are present in both disc- and osseous-form of CSM. A dynamic lesion would be one that worsens or improves with different positions of the cervical spine. Continuous flexion and extension of the cervical spine can lead to spinal cord elongation causing axial strain and stress within the spinal cord, which have been proposed as a key mechanism of spinal cord injury in cervical spondylotic myelopathy in humans. These dynamic changes in the vertebral canal were recently documented in the caudal cervical vertebral region of dogs. Extension of the cervical spine resulted in 28.9% reduction in the diameter of the vertebral canal compared with flexion. Significant narrowing in cervical extension was also demonstrated in the caudal cervical intervertebral foramina. The concept of dynamic compressions is very different from instability, which has been defined as the loss of ability of the cervical spine under physiologic loads to maintain its normal pattern of displacement so that there is no damage to the spinal cord or nerve roots. Instability has not yet been proven in dogs with CSM.
- In addition to the static and dynamic compressions, recent studies have highlighted the importance of molecular mechanisms in animal models and in humans and dogs with naturally occurring cervical spondylomyelopathy. Apoptosis was shown to be present in the spinal cord of dogs with CSM. Apoptosis affected primarily oligodendrocytes. Oligodendrocyte apoptosis can interfere with remyelination and be involved in continuous progression of signs. Blocking the apoptotic pathway lead to improved functional outcome in mice with cervical myelopathy. A study looked at proteomics (protein expression) in the cerebrospinal fluid of dogs with osseous-associated CSM and found upregulation of 2 glycoproteins (alpha-2-HS and SPARC) as well as complement C3, all of which are associated with osteoarthritic changes. Another study looked at the concentration of cytokines in the cerebrospinal fluid of dogs with CSM. There was a significant reduction of monocyte chemoattractant protein-1/chemokine ligand 2 (MCP-1/CCL2) in affected dogs. Monocytes are needed for clearance of axonal and myelin debris, lower concentration of MCP-1/CCL2 may compromise axonal clearance and affect recovery. In the same study higher concentrations of interleukin-6 (IL-6) were found in dogs with spinal cord hyperintensity seen on MRI. IL-6 has been implicated in generation and propagation of chronic inflammation. Studies in humans and rodents have demonstrated that the innate immune response contributes to neuronal and oligodendrocyte death. Further understanding of the molecular and biochemical mechanisms underlying progressive degeneration of the spinal cord and vertebral structures may provide the opportunity to design novel and specific therapeutic strategies to improve long-term outcome of dogs with CSM.

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