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Intervertebral Disk Degeneration in Dogs: Consequences, Diagnosis, Treatment, and Future Directions

N.D. Jeffery, J.M. Levine, N.J. Olby, and V.M. Stein

Evidence of intervertebral disk degeneration (IVDD) is extremely common in dogs, and its prevalence increases with age. It has many important consequences because degeneration of the intervertebral disks often is a prelude to disk herniation, which can injure the spinal cord, spinal nerves, or both. This review summarizes the advances in diagnosis and treatment of IVDD that have been made since the 1950s when the first detailed description of the degenerative changes was published. It also discusses new approaches to treatment of the associated spinal cord injury and new methods by which to classify injury severity that are currently under development.

Key words: Compression; Computed tomography; Contusion; Magnetic resonance imaging; Prognosis; Spinal cord injury.

Intervertebral disk degeneration (IVDD) is an inevitable part of aging and results in a series of progressive pathological changes in structure.[1] However, although this degenerative process can affect the biomechanics of the vertebral column, it would have little clinical importance if it were not that changes in disk contour or escape of its contents frequently injure the spinal cord and associated nerves. Therefore, the primary focus of interest is the damage that is caused, how it can be treated, and how it can be ameliorated or prevented. In this review, we summarize mechanisms of IVDD, highlight variability in patterns of intervertebral disk herniation (IVDH) and associated mechanisms of spinal cord injury (SCI), describe the rationale for current methods of treatment, and introduce advances in diagnosis and treatment that are now in development.

Abbreviations:

CT	computed tomography
DTI	diffusion tensor imaging
IL-1	interleukin-1
IVDD	intervertebral disk degeneration
IVDH	intervertebral disk herniation
IVD	intervertebral disk
MRI	magnetic resonance imaging
NASCIS	North American Spinal Cord Injury Society
NMDA	*N*-methyl D-aspartate
OEC	olfactory ensheathing cell
PEG	polyethylene glycol
SOD	superoxide dismutase
TGFβ	transforming growth factor β
TNFα	tumor necrosis factor α

The Process of IVDD

The normal IVD consists of an incompressible nucleus pulposus, derived from the embryonic notochord, plus the encompassing annulus fibrosus, which, together with the cartilaginous endplates abutting the vertebrae, constrains the nucleus.[2] The incompressible nature of the nucleus together with the ligamentous annulus fibrosus provides a joint between vertebrae that allows limited motion in any plane yet resilience to resist the compressive forces directed along the long axis of the vertebral column that are generated by the abdominal muscles and weight of the head.[3]

The initiating factor for IVDD in humans is thought to be a loss of diffusional capacity of the vertebral endplate blood vessels that provide nutrition for the nucleus pulposus.[4] This decreases the production of extracellular matrix, which predominantly consists of hydrophilic proteoglycans, and consequently alters the mechanical properties of the nucleus, leading to secondary degenerative changes in the annulus fibrosus. Degeneration of the blood supply can arise through numerous mechanisms in humans, but in dogs IVDD is most likely associated with multigenetic predispositions.[5] Some of these may cause vasculopathy, but other incriminated genes appear to be associated with

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selection for chondrodystrophy.[6] Thus, although vasculopathy may be an important pathway in the degenerative cascade, premature senescence of notochordal cells and replacement by chondrocyte-like cells are implicated as a critical mechanism in chondrodystrophoid dogs.[7] DNA microarray analysis of healthy versus degenerate canine disks has suggested that downregulation of canonical Wnt signaling and caveolin-1 expression may be critical steps in the loss of notochordal cell populations.[8]

The pathological features of IVDD in dogs were described in Hansen's classic study published approximately 60 years ago.[3] Hansen described 2 distinct forms of IVDD, each typically occurring in different types of dog. In chondroid degeneration, which occurs predominantly in chondrodystrophic dogs, the nucleus pulposus dehydrates, its cells degenerate, and the whole structure becomes dystrophically calcified. This degeneration changes distribution of intradiscal pressure causing foci of mechanical stress on the annulus fibrosus. With time this abnormal stress can lead to rupture of individual collagenous strands of the annulus until a final mechanical failure, which can occur catastrophically, releases the degenerate nucleus. This extrusion can occur in any direction, but frequently is dorsally directed because the nucleus is eccentrically positioned within the annulus. Hansen associated this type of degeneration with chondrodystrophic dogs and defined the subsequent nuclear herniation as "type I" IVDH.

In fibroid degeneration, which occurs predominantly in nonchondrodystrophic dogs, the annulus is the focus of the degenerative process, although the collagen content of the nucleus increases, sometimes dividing it into lobules. The fibers of the annulus become split from one another allowing accumulation of tissue fluid and plasma. With time, and the mechanical pressure exerted by the nucleus (tending to be more dorsally directed), this degenerative process causes thickening of the annulus, especially dorsally. This can cause the annulus to protrude into the vertebral canal, where it may compress the spinal cord or the spinal nerve roots. This type of IVD degeneration was associated with nonchondrodystrophic dogs and can lead to disk herniation defined as Hansen "type II." More recent histologic analysis, although generally supportive of Hansen's original descriptions, has suggested that there is less difference between degeneration in chondrodystrophic and nonchondrodystrophic dogs than was previously assumed.[9,10] Specifically, the more advanced stages of annulus fibrosus degeneration in nonchondrodystrophic dogs has shown replacement of notochord-like cells with chondrocyte-like cells similar to the process that occurs in chondrodystrophic dogs.

From a clinical standpoint, the pathological distinction made by Hansen has in general withstood the test of time; most cases of clinically relevant IVDH can be classified into 1 of these 2 types of syndrome. Nevertheless, some cases of IVDH do not fit neatly into one or the other of these categories. It is commonplace to observe portions of torn annulus within the vertebral canal of both chondrodystrophic and nonchondrodystrophic dogs. Furthermore, clinical signs can appear rapidly in association with type II IVDH, and chronic clinical signs can be associated with type I IVDH. Moreover, there has been some controversy about which dogs can be considered chondrodystrophic because Cocker Spaniels[3,11] and Beagles[12] often are included in this group despite the lack of characteristic stunted limbs.

Consequences of IVDD

Origin of Clinical Signs Associated with IVDD

Although the process of IVDD is extremely common, especially in chondrodystrophic breeds, most affected dogs exhibit no external evidence of this degenerative process. When clinical signs do occur, they usually result from impingement of the degenerating disk on neural structures, which can cause both pain and neurological dysfunction of varying severity.[2] Stretching of fibers of the dorsal annulus or of the dorsal longitudinal ligament also may cause pain by activation of the rich nociceptive innervation that these structures contain.[13]

When clinical signs do occur, they can result either from (1) stretching the fibers of the dorsal annulus or of the dorsal longitudinal ligament, which can cause pain by stimulation of their nociceptors[13]; or (2) impingement of the degenerating disk on neural structures, which can cause both pain and neurological dysfunction of varying severity.

The term IVDH can be used to summarize mechanisms by which a degenerating disk can cause pain and neurologic deficits, and is defined as localized displacement of the intervertebral disk beyond the normal 3-dimensional anatomic limits of the disk.[14] This then can be broadly divided into 2 subtypes (ignoring Schmorl's nodes, which appear to be of uncertain clinical relevance in dogs[15]), each associated with different types of IVD degeneration: (1) extrusion of the degenerate nucleus (type I) or (2) protrusion of the degenerating annulus into the vertebral canal (type II). These 2 events imply different modes of injury to the spinal cord. Nuclear extrusion results in a mixed *compressive* and *contusive* lesion, the proportions of each variable depending on the volume of material and the rate at which the extrusion occurs. Thus, the end result can vary between almost entirely contusive to almost entirely compressive. In contrast, annular protrusion usually, but not exclusively, occurs over a period of months to years and thus causes a slowly progressive compression of the adjacent spinal cord. However, because of motion of the vertebral segments, it also can be accompanied by dynamic compression in which compression varies in severity from moment to moment depending on the instantaneous position of the vertebrae (Fig 1).

Other Types of IVDH

Recent increase in the use of MRI to diagnose lesions of the canine vertebral column has allowed identification of a wider range of disk-associated

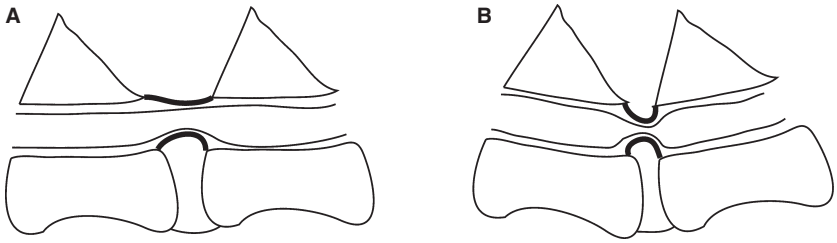

Fig 1. Line diagrams to illustrate dynamic compression associated with intervertebral disk protrusion. **(A)** In the resting state, protrusion of the dorsal annulus is causing mild spinal cord compression. **(B)** During spinal dorsiflexion, spinal cord compression is exacerbated. The flaval ligament dorsal to the spinal cord also may contribute to cord compression during dorsiflexion.

injuries to the spinal cord. Most notable among these is peracute extrusion of apparently normal IVD nucleus presumed to be associated with supraphysiological, mechanical stress during athletic activity.[16–18] A portion of the nucleus is explosively expelled through the annulus and its displacement can readily be observed on MRI. This type of disk extrusion also sometimes has erroneously been referred to as "type III" IVD, but this term should not be used because such cases display no evidence of preexisting disk degeneration. Instead, Hansen used the term traumatic disk prolapse.[3] The injury to the spinal cord associated with these explosive lesions varies widely, but can be very severe (see below).

A similar, but distinctly different, lesion has been described in the cervical region of dogs, in which material appearing hyperintense on T2W MRI scans is observed ventral to the spinal cord (Fig 2).[19] The radiological interpretation, supported by surgical findings in some cases, is that the material is extruded hydrated nuclear material and may be associated with moderate spinal cord compression; the severity of associated SCI is variable.

Contusion

Contusion injury is the better understood of the injury mechanisms associated with IVDH because it has been relatively easy to reproduce in the laboratory.

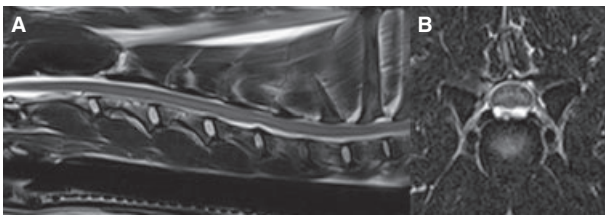

Fig 2. T2-weighted MR images from a dog with acute onset nonambulatory tetraparesis and ataxia localized to the cervical spinal cord. **(A)** Sagittal images detect focal ventral extradural spinal cord compression dorsal to the C5–C6 disk space with associated disk space narrowing and partial loss of normal T2 nuclear signal. **(B)** Transverse image through C5/C6 IVD illustrating hyperintense material ventral to the spinal cord with a "seagull-like" appearance. These MRI features are consistent with hydrated nucleus pulposus extrusion, which was confirmed surgically (also see ref. 18).

The earliest model (incidentally, conducted in experimental dogs) was a weight drop method in which a defined mass was dropped a defined distance onto the exposed spinal cord and then removed.[20] This method has been refined considerably in the intervening decades and models now rely on computer-controlled spinal cord impact, almost exclusively in laboratory rodents, in which velocity, force, and duration of contusion all can be varied,[21,22] and which also incorporate feedback information to ensure reproducibility of impact force and consistency of injury.[23,24]

These laboratory animal models have provided the core knowledge from which to infer the biochemical and cellular processes that occur in SCI in clinical patients and have been reviewed in many basic science, medical, and veterinary publications.[25–27] Minor, localized axonal injury can be detected immediately after spinal cord contusion and there is evidence of vascular injury, including breaching of the blood–spinal cord barrier, but little immediate structural disruption. This primary injury then is followed during the succeeding few (approximately 7) days by an evolving secondary lesion, triggered by the immediate vascular (vasoconstriction plus extravasation of cells and plasma into the neuropil) and cellular responses that cause progressive tissue damage, culminating in loss of neurons, oligodendrocytes, and axons, and eventual replacement of the destroyed tissue by tissue fluid, reactive astrocytes, or both. Mechanisms underlying this secondary injury have been elucidated during the previous 2 decades by laboratory investigations, and provide the basis for hope that interventions in the future may ameliorate the progressive destruction of spinal cord tissue that, currently, inevitably follows contusive injury.

A key pathological event of contusion injury is calcium entry into neuronal cell bodies, axons, astrocytes, and oligodendrocytes. This activates a wide range of enzymes, such as calpains and caspases, that activate autodestructive pathways and can result in apoptosis or necrosis.[28,29] The end results of this process also have been illustrated in studies conducted on euthanized veterinary patients.[30] Free radicals are released by enzymatic destruction of mitochondrial membranes, activated microglia,[31] and activation of neuronal nitric oxide synthase and cause progressive damage to cell membranes and additional cycles of cell death. Activated inflammatory signaling pathways drive inappro-

priate vascular tone and infiltration of inflammatory cells into the neuropil. Microglial activation appears to be a prominent event in dogs with naturally occurring SCI,[31,32] and cytokine release from this cell population may be important in directing innate inflammatory events.[32] In particular, IL-1, TNFα, and nitric oxide are incriminated in damage to neurons and oligodendrocytes; however, there is also evidence that microglia also may play protective roles in SCI.[32,33] For instance, microglia also produce TGFβ, which has neuroprotective effects, and there is direct evidence from in vivo studies that transplantation of activated macrophages can be associated with axon regeneration and functional improvement.[34] Neutrophils accumulate in the early stages and cause cell death directly because they produce free radicals that destroy cell membranes. These are followed by lymphocytes that become autoreactive, having been exposed to previously hidden antigens in the CNS.[35] On the other hand, there is also evidence of beneficial effects of T-cell–mediated responses to myelin-derived autoantigens,[36] suggesting a fine balance between damage and protection that may depend on factors that are as yet incompletely understood.

Calcium entry is dependent initially on cell depolarization (because of direct injury), allowing sodium entry which then is exchanged for calcium, especially in axons. Cell depolarization also releases excitatory neurotransmitters, notably glutamate, that can in turn allow calcium entry via NMDA receptors. Glutamate in excess is toxic by this process, termed excitotoxicity. Destruction of oligodendrocytes (which are especially vulnerable because of their large membrane areas and NMDA receptors) will lead to demyelination of axons, which in turn renders them more susceptible to destruction.[37]

Eventually homoeostasis is restored by astrocytic responses, forming a new *glia limitans* and restoring the blood–spinal cord barrier. The end result is the formation of a glial scar consisting of reactive astrocytes plus a heavy deposition of chondroitin sulfate and keratan sulfate proteoglycans, all of which are highly inhibitory to regeneration of axon processes, thus preventing restoration of damaged connections across the damaged area. Typically, preserved tissue (if there is any) is located at the periphery of the spinal cord.[38–40] This appearance suggests that the more central regions are more susceptible to contusive injury, perhaps because blood vessels in the gray matter are more easily damaged, and the inner part of the white matter is at a watershed area between blood supplied by the peripheral arteries and that supplied by the central ventral artery.[41] There is also evidence that CNS gray matter has a greater energy requirement than white matter,[42] making it more susceptible to interruption in blood supply associated with injury.

Clinical Signs of Contusion

Typically, contusive injury is associated with a rapid loss of neurologic function, occurring during a period of seconds to minutes. However, in association with IVDH the clinically observable events may occur over a period of minutes to days, depending on the rate at which the nucleus extrudes. Localization of the lesion usually is straightforward, based on the typical constellation of clinical signs to be expected with a transverse myelopathy at the specific location. In some acute cases, the clinical picture can be complicated by spinal shock, in which spinal reflexes caudal to a severe acute lesion may be depressed (sometimes for as long as several days), although this depends on the species (and the definitions used). This clinical appearance can create confusion regarding accurate lesion localization because limb reflex depression suggests a lesion within a spinal intumescence. For instance, after a severe thoracolumbar injury, the pelvic limb flexor reflexes in dogs can be depressed or even absent for up to 24 hours.[43] Close examination of the cutaneous trunci (panniculus) reflex can aid in accurate lesion localization in such cases. Changes in coordination of the micturition reflex that occur during the first several weeks after thoracolumbar SCI are sometimes also a reflection of resolution of spinal shock.

Myelomalacia may spread cranially and caudally from the epicenter of the injury and in some cases will ascend and descend many segments, which can be fatal. It is most common after severe acute thoracolumbar cord contusion and may affect approximately 10% of dogs in which there has been complete loss of pain sensation from the pelvic limbs.[44] The mechanism by which ascending myelomalacia develops is not completely understood, but it appears to be a consequence of ischemia, probably resulting from vasospasm and thrombosis.[45] The typical clinical signs of ascending and descending myelomalacia include loss of initially intact spinal reflexes, including flexor reflexes in the thoracic and pelvic limbs, respiratory distress, and, finally in many cases, death as a result of respiratory paralysis. Warning signs of its impending development, such as decreased body temperature and ascending cutaneous trunci (panniculus) reflex cutoff, can be detected within about 2 days of the injury.[46] There is no treatment for this condition, and distressed affected dogs should be euthanized.

Spinal Cord Compression

Although spinal cord compression is common in both humans and veterinary species, it has been subject to surprisingly little laboratory investigation. It has long been known that chronic compression will lead to axonal loss, with evidence of Wallerian degeneration in the segments distal to the lesion, and in general, it would appear that white matter damage is most prominent. The mechanisms by which this occurs have not been elucidated but have been assumed to be caused by poor blood flow owing to the increased pressure within the pial boundaries. However, there is also evidence from in vitro studies that mild compression can cause a reversible conduction block, probably mediated by changes in membrane permeability.[47]

Prolonged spinal cord compression in experimental animals has been associated with demyelination.[48]

In 1969, Wright and Palmer[49] described the histological appearance of spinal cord that had been compressed for a long period of time and deduced that impairment of venous drainage was responsible for poor blood flow through the affected lesion. In a more recent experimental study in dogs, al-Mefty et al[50] reported that the epicenter of damage was in the watershed regions of the spinal cord, at the junction between the region supplied by the peripheral arteries, and the ventral spinal artery. Therefore, in this model, the most damaged area appeared to be at the periphery of the gray matter, but affecting both gray and white matter. However, this model used incremental pressure increases to produce long-term compression, and involved the cervical region, suggesting that dynamic compression also may have played an important role. In contrast, other models[51,52] exhibit a progressive loss of gray matter with time and compression, suggesting that the distribution of damage with chronic compression includes both gray and white matter. Evaluation of pathological material from dogs in which there has been chronic disk protrusion (Fig 3) supports this viewpoint.

Clinical Signs of Spinal Cord Compression

Spinal cord compression caused by type II IVDH classically is associated with an insidious onset of clinical signs. Owners typically report a loss of function occurring over a period of weeks to months, often with periods in which a step-like acute worsening occurs. The signs depend on localization of the lesion and may include both gray and white matter deficits, and usually progress very slowly. Signs of pain may be reported by the owners, although these are not likely to reflect spinal cord compression (because the spinal cord parenchyma contains no nociceptors), but may reflect stimulation of nociceptors in the annulus or arise because of nerve compression.

Lesions of the Spinal Nerves

Intervertebral disk herniation also may cause peripheral nerve injuries because of the proximity of the spinal nerves to the intervertebral disks. Although contusive injuries to nerves can occur as a result of IVD lesions, the effects are self-limiting, whereas compression is more common and more difficult to manage. There are 2 main anatomical sites at which nerve compression can occur—the vertebral canal in the lumbosacral region and the foramina at any intervertebral space. Nerves in the intervertebral foramina are susceptible to compression if an IVD herniates laterally rather than dorsolaterally and occasionally may compress the nerve lateral to the foramen. Spinal nerves commonly are compressed in type I TL IVDH and this constitutes a likely source of pain. In the cervical or lumbosacral regions, lateralized disk extrusions may cause lameness or limb pain because of nerve compression. In the lumbosacral region, single or many nerves of the cauda equina can be compressed within the vertebral canal, causing various clinical signs associated with deficits in function of the caudal lumbar, sacral, and caudal nerves. Lateralized IVD lesions also can occur in the lumbosacral region, and such affected animals typically present with lameness rather than typical neurologic deficits that may lead owners to consult orthopedic specialists. Nerve compression can be exquisitely painful, and this type of lesion should be suspected in animals that present with "screaming pain," even without other localizing signs.

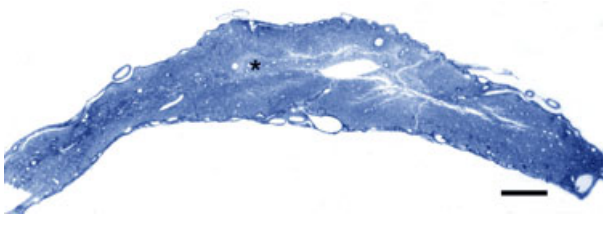

Fig 3. Transverse semithin section through region of chronic spinal cord compression, illustrating gross loss of gray matter; *indicates the sole remaining region of gray matter (dorsal horn). There also is substantial loss of white matter area and axonal integrity. Toluidine blue, scale bar: 500 mm.

Differential Diagnosis

The variable onset and progression of clinical signs related to IVDH mean that there frequently is a long list of possible diagnoses for affected animals. Although IVDD occurs throughout the vertebral column, the sites at which IVDH is recognized as a clinical problem are relatively limited. In the thoracolumbar segment, about 75–80% of acute IVDH occur between T11 and L1 disk spaces,[53,54] and a similar proportion of acute cervical IVDH are located from C2 to C4.[55,56] Chronic IVDH is most common in the caudal cervical,[57] thoracolumbar junction,[58] and L7/S1.[59] The thoracolumbar junction region is thought to be susceptible because it lies at the junction between the heavily muscled (and therefore relatively rigid) lumbar region and the rigid thoracic cage.[3] There are also changes in the orientation of the articular facets of the synovial joints within this area.[60] The predisposition of the caudal cervical region to chronic IVDH has been attributed to the increased rotational forces that can be applied to those IVD owing to the orientation of the articular facets.[61] The lumbosacral region may be susceptible because it is the focus of locomotor forces transferred from the pelvis to vertebral column,[59] and there is also a high incidence of congenital deformities at this intervertebral space, which have been associated with symptomatic IVD lesions.[62]

In general, 3 syndromes associated with symptomatic IVDD can be identified: pain, acute and chronic ataxia, and paresis. The differential diagnoses for each of these are summarized in Table 1. For animals presenting with apparent signs of vertebral column pain, there are many possible alternative causes, including abdominal diseases (because animals with abdominal

pain will commonly tense their abdominal muscles in the same way as animals with spinal pain) and various inflammatory, infectious, or neoplastic diseases (of which there are many) of any axial musculoskeletal structure. Narrowing down the list of differential diagnoses is dependent on careful examination, aiming to precisely localize the site, and judicial use of the signalment and historical information.

For animals presenting with acute paresis or ataxia, the most common differential diagnoses are lesions that will produce instability of the vertebral column, such as pathologic or traumatic fractures, ischemic myelopathies, and myelitis. Neoplastic lesions can cause acute onset of clinical signs in the spine because, although the neoplastic process proceeds slowly, associated pathological fractures or vascular compromise occurs acutely. In particular, tumors with a high mitotic index can rapidly increase in size and result in acute spinal cord vascular thrombosis or rupture. There are many other possible causes for acute paresis or ataxia (see Table 1), and there is the potential for confusion with lesions of the peripheral nervous system for deficits associated with the spinal intumescences (because these can produce clinical signs of flaccid paresis, sensory loss, or both).

For animals presenting with chronic paresis or ataxia, the main differential diagnoses are other compressive lesions, especially neoplasia, or degenerative conditions affecting the CNS, such as degenerative myelopathy. Difficulties can arise in differentiating degenerative myelopathy from type II IVDH, especially in middle-aged German Shepherds, because individuals may be simultaneously affected by both conditions. In such cases, in which type II disk-associated spinal cord compression has been diagnosed by advanced imaging, testing for the SOD1 mutation[63] can be helpful to determine whether the dog is also at risk for degenerative myelopathy. For cases that are both at risk of degenerative myelopathy and have type II disk herniation, trial treatment with corticosteroids also may be useful because this will, at least partially, alleviate the clinical signs associated with spinal cord compression, but have no effect on those caused by degenerative myelopathy. The high prevalence of SOD1 mutations in normal individuals of some breeds[64] can make interpretation of genetic tests alone challenging in the absence of neuroimaging.

Imaging

After localization, imaging is usually the best next diagnostic step; it can provide further information on the severity and nature of the lesion and can frequently rule in or rule out diagnoses. For dogs presenting with pain alone, plain radiographs may be sufficient to initially rule out lesions causing gross bone destruction (such as discospondylitis or neoplasia), allowing symptomatic treatment for IVDH to be instituted. However, persistence of pain is an indication for advanced imaging. Plain radiographs frequently will demonstrate changes that can be associated with symptomatic IVDH, such as decreased distance between vertebral end plates, disk space wedging, and reduction in space between articular processes, but is rarely able to provide sufficient information for definitive diagnosis.[65]

Table 1. List of well-recognized causes for specific clinical presentations that may be caused by intervertebral disk herniation.

	Cervical	Thoracolumbar	Lumbosacral
Pain alone	Acute IVDH Nerve root compression Neoplasia Meningitis Fracture–luxation	Acute IVDH Neoplasia Meningitis	Nerve root compression Neoplasia Iliopsoas muscle injury Meningitis
Acute paresis/ataxia	Acute IVDH Fracture–luxation Neoplasia MUE	Acute IVDH Vascular lesion Neoplasia (esp large breeds) Fracture–luxation MUE (uncommon)	Fracture–luxation IVDH (uncommon) MUE (uncommon) Vascular lesions
Chronic ataxia/paresis	Chronic IVDH Neoplasia Vertebral anomalies	Chronic IVDH Degenerative myelopathy Neoplasia Hemivertebra Arachnoid scar (pugs)	Chronic IVDH OCD lesion (young dogs) Neoplasia
Nonspinal distractors	LMN lesions (in PNS) Hypoadrenocorticism Other metabolic lesions Cardiomyopathy Junctionopathies	Acute bilateral CCLR	Aortic thrombosis Calcaneal tendon rupture LMN lesions Bilateral hock lesions (OCD) Iliopsoas muscle injury Junctionopathies Bilateral CCLR

CCLR, cranial cruciate ligament rupture; IVDH, intervertebral disk herniation; LMN, lower motor neuron; MUE, meningoencephalomyelitis of unknown etiology; OCD, osteochondrosis dissecans; PNS, peripheral nervous system.

In the past, myelography routinely was used to define the affected region and make a definitive diagnosis of IVDH. Myelography is useful to distinguish a region of spinal cord that is apparently swollen (as occurs in contusive injury), and also for identifying regions of deviation in the subarachnoid space that can be used to deduce the location of extruded nucleus or protruded annulus. Today, cross-sectional imaging using MRI and CT has superseded other techniques because of the superior information provided.[66,67]

Magnetic Resonance Imaging

Magnetic resonance imaging is unrivaled in its ability to show detail of the spinal cord parenchyma, and after contusive injury will disclose regions of hyperintensity on T2W scans that can be correlated with the region in which the blood–spinal cord barrier has been compromised (the hyperintensity is assumed to be a consequence of edema, necrosis, or hemorrhage). In addition, there is evidence that the extent of T2W hyperintensity after an acute disk extrusion can have prognostic value.[68,69] Specific sequences can be used to identify regions of hemorrhage,[70] and, recently, diffusion tensor imaging, which measures the direction and magnitude of water diffusion, has been introduced into veterinary imaging and may provide better definition of regions of white matter injury and their severity (Fig 4).[71–73] In spinal cord white matter, water diffusion is highly anisotropic, meaning that water diffuses predominately in the craniocaudal or caudocranial direction, parallel to the myelinated axons. Decreased diffusion anisotropy indicates demyelination, axonopathy, or both, and may serve as an indicator for functional motor recovery.

The availability of cross-sectional images also means that it is possible to define the relationship between extruded nucleus or protruded annulus and the spinal cord. However, because heavily calcified material is poorly visible on MRI scans, this is not as clearly defined as on CT images. Different types of disk-associated lesions can be defined, including bulging, protrusion, and extrusion.[74]

Computed Tomography

Computed tomography imaging has the advantage of being exquisitely sensitive to changes in radiographic density, thus allowing definition and high spatial resolution of calcified nuclear material within the vertebral canal or intervertebral foramina. It also provides a cross-sectional image that allows very clear definition of the circumferential location of the extruded or protruded material with respect to the spinal cord. Its drawback in diagnosis of type I IVDH is that extruded material may not be heavily calcified, or may be of small volume, and therefore may be difficult to detect, which may account for its decreased sensitivity to acute disk herniation compared with myelography in some reports.[75] Furthermore, hemorrhage associated with disk extrusion is not clearly differentiated from spinal cord.

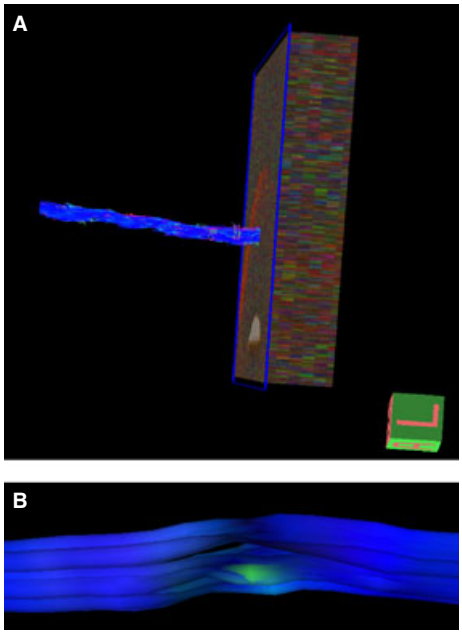

Fig 4. Diffusion tensor tractography. **(A)** The blue tracts extending to the left, away from the multicolored 3-dimensional volume, are a graphical depiction of water diffusion in the spinal cord. This depiction is created by computer algorithms based on diffusion anisotropy and direction of diffusion. Diffusion data are color encoded such that blue represents highly anisotropic diffusion in the craniocaudal plane. **(B)** Extruded intervertebral disk material has disturbed the main water proton diffusion direction (craniocaudal = blue) and this is indicated by a green color change. Compression of the spinal cord at this level is recognized as thinning of the visually represented tissue.

Overall, the choice between these modalities in diagnosing symptomatic IVDH relies on deciding whether imaging the spinal cord or the compressing material itself is of greatest importance. On the whole, in mild-to-moderate SCI, the most important goal is to accurately localize extruded material so that a surgical procedure to access and remove it can be planned. This can be achieved by CT in most cases, but MRI provides a critical advantage in detecting nonmineralized compressive material such as that primarily consisting of hemorrhage, or type II IVDH. In severe SCI, if there has been injury of sufficient severity for the dog to lose deep pain sensation, it is of utmost importance to identify any region of SCI and its extent because the prognosis for these animals generally is uncertain and treatment must be tailored precisely to the needs of the individual. On occasion, there may be severe spinal cord MRI intensity changes on images acquired at sites distant from disk extrusion (see Fig 5), and sometimes MRI can suggest a lack of need for surgical intervention, because some such cases have no apparent extradural compressive lesions.

The Fate of Extruded IVD Nucleus

Intervertebral disk nucleus that is extruded into the vertebral canal loses its source of nutrition and is

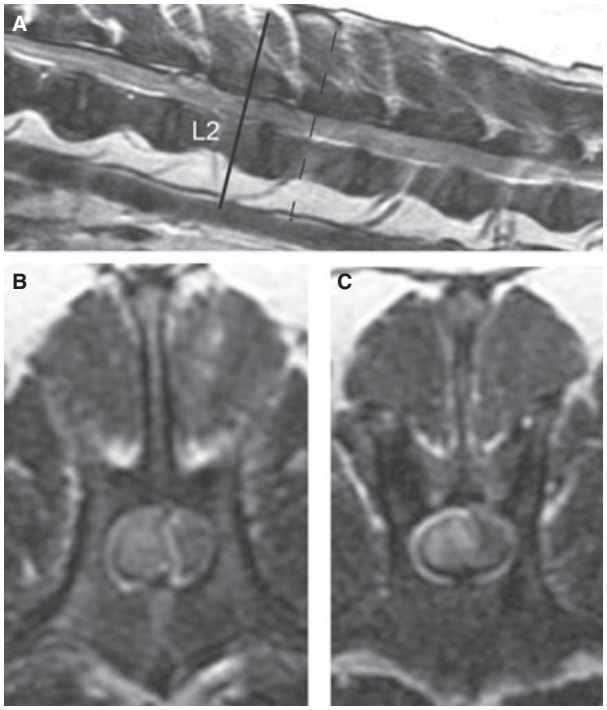

Fig 5. MRI images of the spinal cord of a dog with a severe spinal cord injury illustrating how T2-weighted images provide invaluable information regarding spinal cord injury associated with IVDH. **(A)** Midsagittal image showing minimal evidence of IVDH at L1/2. **(B)** Transverse image at level of solid line in (A), illustrating moderate spinal cord compression. **(C)** Transverse image at level of dashed line in (A), illustrating gray matter hyperintensity associated with milder spinal cord compression. This dog was euthanized with signs of ascending myelomalacia 3 days after these images were acquired.

frequently termed "sequestrated" in human medicine.[14] If not removed surgically, it can undergo cycles of hydration and dehydration, which can account for changes in its volume observed on MRI scans.[76] Over longer periods of time, it can become revascularized[77] and undergo macrophage invasion[78] accompanied by an upregulation of MMP expression,[79] all of which would be expected to result in partial clearance and eventual incorporation into the contours of the vertebral canal. There is evidence in humans that the MRI appearance, specifically rim enhancement, can be predictive of disk extrusions that will decrease in size over time.[80]

Treatment of Symptomatic IVDD

Treatment of IVDD is a vast topic that has generated much controversy over the years. However, to a large extent, there is now a consensus of opinion, although the evidence on which this consensus has been built is not as strong as desirable. The controversy arises because there is a marked tendency for spontaneous recovery of function after injuries to the nervous system, and therefore there is argument over the extent to which surgical intervention is necessary to aid in recovery. The other difficulty is the variability in presenting clinical signs and whether they are recurrent or first-time occurrences, all of which may affect the treatment decision. Here, we discuss the options depending on the nature of the inciting injury.

Contusion Injuries

There is no medical or surgical intervention that is unequivocally established to improve the functional outcome after spinal cord contusion—apart from maintenance of blood pressure within normal limits.[81] This lack of effective treatment persists despite intense research into the mechanisms of contusive SCI during the past 3 decades. During the early 1990s, there was optimism that methylprednisolone sodium succinate (MPSS) given at a high dosage within 8 hours of the injury might ameliorate functional loss. The evidence was accumulated from experimental work in rodents and appeared to be confirmed by a series of randomized clinical trials in human subjects, notably North American Spinal Cord Injury Society (NASCIS) II.[82] However, since these publications there has been a steadily increasing distrust of the study conclusions, based on baseline differences between groups and questions regarding the validity of the assessment measures[83,84] and also consideration of the possible adverse systemic effects of high-dose corticosteroid therapy.[85] In veterinary medicine, there is even more reason to be distrustful of the NASCIS results because the improvement in outcome that was claimed was mainly dependent on improvement in gray matter function, whereas the target in most veterinary IVDH is white matter recovery (because of the regions of the cord that are predominantly affected). Furthermore, a small study in experimental dogs[86] failed to detect any improvement over placebo after MPSS, although this also could be a result of type II error.

Management of spinal cord contusion injuries therefore consists of nursing care to aid in bladder emptying if required, plus rehabilitation exercises designed to accelerate recovery—although there are as yet no data to support their effectiveness. There are numerous possible complications of severe contusive injuries, such as pneumonia, decubital ulcers, and urinary tract infection, and management care is focused on these aspects. The time needed for recovery varies among individual animals and depends on severity and site of the lesion, but the full recovery period is at least 3 months. It is common for severely injured animals that still eventually make nearly total recoveries to show no change in neurologic status for 7–10 days after injury. Some contusive injuries are of sufficient severity to preclude functional recovery. These currently are difficult to identify at the time of injury, although they will have loss of deep pain sensation soon after the impact. Methods to identify these cases currently are being investigated (eg, markers in CSF or blood), and those that do not recover with conventional treatment are targets of novel approaches aiming to restore lost function in dogs in the chronic stage of persistent paralysis (see below).

Spinal Cord Compression

Spinal cord compression caused by IVDD can be treated medically or surgically. There is obviously a clear rationale for surgical treatment—the compression can be relieved by various surgical approaches that depend on the type and location of lesion.[87,88] However, it is well recognized that the spinal cord is able to function satisfactorily even when it is compressed to some degree, although there appears to be a threshold level of compression at which its function becomes rapidly compromised. Therefore, the question arises as to how much compression justifies a decompressive surgical procedure, and this is the most controversial aspect of treatment of IVDD. Here, considerations in treating type I and type II disk lesions are discussed separately.

Compression Associated with Type II IVDH

The clinical signs associated with type II IVDH are progressive over months and frequently are associated with moderate-to-severe compression that may be exacerbated by a dynamic component—especially in the cervical region. These cases are clear candidates for surgery because there is little prospect of the clinical signs improving spontaneously. The lesion develops slowly and is seldom associated with a substantial inflammatory component that could resolve spontaneously. However, the choice often is complicated by uncertainty regarding the rate of progression. Many affected animals are middle aged or older, and if the condition is only slowly progressive it is uncertain whether it is worthwhile to remove the compression. Recent evidence regarding the natural history of dogs with type II IVDH in the cervical spinal cord has clarified this issue, suggesting that over a period of 12–18 months there appears to be little benefit of surgery.[89] There are no comparable data available for thoracolumbar IVD protrusions. On the whole, the decision for individual dogs affected by TL type II IVDH is made after consulting with the owner about their expectations for the individual dog's quality of life and potential to recover or suffer injury. In large-breed dogs, and German Shepherds especially, it is also important to consider the possibility of concurrent degenerative myelopathy.[63] The outcome after surgical decompression for type II IVDH is frequently very gratifying, especially when the disk is excised using corpectomy,[90,91] although unfortunately there is often a risk of recurrence at another site because affected animals often have many protruding disks.

The main alternative treatment for chronic compression is corticosteroids, used at anti-inflammatory dosages. These drugs decrease vascular permeability and therefore decrease the accumulation of edema fluid within the compressed tissue, thus alleviating clinical signs associated with compression.[92] However, this possible benefit must be weighed against the development of the deleterious effects of corticosteroid therapy, of which muscle wasting and weight gain are most detrimental in paretic dogs.

Spinal Cord Compression Associated with Type I IVDH

When an IVD extrudes the nucleus, the spinal cord suffers a combination of contusion and compression, and the extent to which each is responsible for the observed clinical signs will vary among individual dogs. In some, often more chronically developing cases, there can be extremely large compressive lesions associated with type I extrusions, often with surprisingly little in the way of accompanying clinical signs (see Fig 6). Such animals often exhibit considerable spinal pain, and for this reason alone they may be candidates for surgical decompression.[93]

Dogs in which extrusion has occurred rapidly are more common. In such cases there is often considerable accompanying hemorrhage and spinal cord inflammation and edema, combined with the compression. The question in this situation is how much compression, when in combination with contusion, is sufficient to justify decompressive surgery. This question was first addressed by veterinarians in the 1950s and 1960s, when comparisons of outcome between surgery and conservative treatment were made.[94,95] The conclusion was, in general, that decompressive surgery was preferable because a greater proportion of animals recovered the ability to walk. The evidence, however, was of poor quality by modern standards of veterinary publications, mainly because the selection criteria were poorly documented. Where it is possible to analyze the data further, the discerned benefit of surgery applied both to dogs that retained voluntary movement of the pelvic limbs and also those that had lost sensation.[94] The surgical techniques and medical management that were used in those early studies are quite different from those in common use today, and so it cannot be assumed that the difference in outcome between surgical and conservative treatment will be of similar magnitude to these initial studies.

More recently, Levine and coworkers have examined the outcome after conservative treatment for dogs diagnosed with clinical signs presumed to be referable to IVDH in the thoracolumbar or cervical regions.[96,97] Their findings confirm earlier data, eg,[98] suggesting that conservative treatment is in general successful. Approximately 50% of dogs improved from their presenting neurologic status with no recurrences over a prolonged follow-up period, with treatment failure of approximately 15–20%. This level of treatment failure has been cited by many as a reason to recommend surgery for every dog with clinical signs of IVDH. However, owing to study design constraints, the cases in these studies deemed treatment failures would not necessarily have failed to recover with continued conservative treatment.[98] Instead, at that point, the owners made a decision to opt for euthanasia or surgery. In addition, examination of a population of similar, or even more severely injured, dogs treated surgically indicates that closer to 90% make a successful recovery.[99,100] The current consensus of opinion is therefore that decompression is warranted to accelerate and

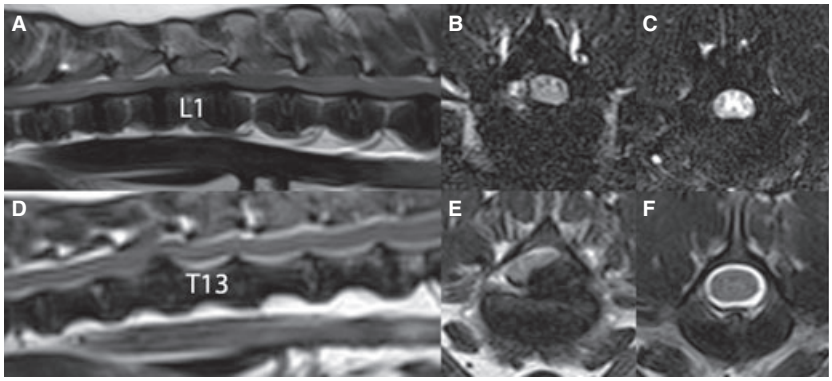

Fig 6. T2-weighted MR images from 2 dogs with thoracolumbar intervertebral disk extrusion to illustrate the variable relationship between compression and severity of neurologic deficits: Dog 1 **(A–C)** was paraplegic with absent pain perception from the pelvic limbs. (A) The midsagittal image suggests that there is minimal spinal cord compression. (B) Transverse T2-weighted fat saturated image at the epicenter of disk extrusion (L1/2 IVD) confirms the lack of compression and highlights hyperintensity of gray matter, which often is associated with contusive lesions. (C) Transverse T2-weighted fat saturated image over the L3 vertebral body illustrates the extensive craniocaudal spread of gray matter hyperintensity that can occur in severe contusive injury. Dog 2 **(D–F)** was ambulatory with paraparesis and pelvic limb ataxia. (D) Sagittal images suggest marked spinal cord compression resulting from focal disk extrusion. (E) This suspicion is confirmed on transverse image over the epicenter of IVDH (at T12–T13), also illustrating the laterality of the lesion—a common feature of type I IVDH. Spinal cord hyperintensity was not apparent at the site of compression (E), or at adjacent, noncompressed spinal cord segments (at L1/2) (F).

provide more extensive recovery in dogs that are nonambulatory and, sometimes, to alleviate pain in ambulatory patients. Therefore, although randomized trials to quantify the value of surgical intervention have not been carried out, the absence of equipoise unfortunately imposes a severe ethical obstacle to reexamination of the controversy.

There is some good evidence from experiments in laboratory rats[101] in which the spinal cord was subjected to contusive injury and subsequently to compression of varying degree to support this consensus opinion. These data suggest that compression of <50% of the spinal cord diameter may not be associated with long-term loss of function, although it is difficult to interpret directly because the magnitude of contusive injury also will vary in clinical cases. Furthermore, the data suggest that rapid decompression is beneficial, although the effect is minimal if decompression is not carried out within approximately 6–8 hours of injury, which may not always be practical in clinical patients. Recent clinical investigations[102,103] in human patients suffering from spinal fractures also have confirmed that rapid decompression is beneficial, although it is important to note that in this context in human medicine "rapid" means within 3 days.

Nerve Compression

Nerve compression arising from IVD lesions commonly causes extreme pain and may also produce observable neurologic deficits, depending on the site of the lesion. Nerve decompression is frequently imperative on humane grounds because of the pain. Less severely affected individuals can be managed using anti-inflammatory drugs or gabapentin. At the lumbosacral junction, compression of components of the cauda equina may cause ill-defined back pain that can be managed by conservative or surgical means. Except for patients with severe neurologic deficits, it is currently unclear which patients should be selected for surgical treatment. It has been suggested that prolonged incontinence associated with chronic compression may carry a poor prognosis.[104] There is a similar controversy regarding treatment of human patients with lumbar disk protrusions. Although there have been many trials comparing surgical and medical treatment, meta-analysis suggests that there is little to support one modality over the other, especially when outcome is assessed at >12 months after presentation.[105]

Management of Recurrent Clinical Signs Associated with IVDD

Most animals that suffer clinical signs associated with IVDD are at risk of future episodes of disk-related symptoms because the degenerative process, although it may cause clinical signs at one site on one specific occasion, is a multisite disease. Therefore, clinical signs can recur because of progression of degeneration at the same site or, more commonly, at multiple alternative sites. The clinical signs associated with recurrence can vary from mild spinal pain to deep pain-negative paraplegia that may later prove irreversible. There is a known risk of recurrence after decompressive surgery alone, although the reported proportions vary widely from study to study.

Fenestration

Intervertebral disk fenestration has been used for many decades as a method to remove the IVD nucleus

from its normal anatomical position and thereby reduce the risk of future damaging herniations into the vertebral canal. There has been considerable controversy regarding its effectiveness, but a recent trial has clearly demonstrated the benefits in dogs that had previously suffered type I thoracolumbar IVDH of sufficient severity to require decompression. The risk of recurrence was decreased approximately from 17% to 7%.[106] This finding also is supported by comparing outcomes of observational studies in which dogs either did or did not undergo routine fenestration after decompressive surgery for type I TL IVDH.[53,107] Although this benefit has been clearly defined, some surgeons are reluctant to carry out the procedure because of the perceived risks of neural or vascular injury, increased surgical time, and risks of infection. However, these risks, which appear to be low,[54] also have to be balanced against the finding that, of dogs that suffer recurrence of clinical signs of IVD extrusion, approximately 50% will be euthanized by their owners because of treatment cost and perceived animal suffering.[53]

Fenestration also has been advocated for prophylaxis of cervical disks, but this indication has not been so popular. Recurrence of clinical signs after cervical disk extrusions following one episode of surgical decompression is uncommon,[108] which perhaps has impeded use of the procedure for this purpose. On the other hand, fenestration also has been attempted as a treatment for type II IVDH in the cervical region,[109] for which it was notably unsuccessful. The reason for deterioration after fenestration of type II disk protrusions likely is because the fenestration procedure, by removing the central component of the IVD, allows collapse of the disk space. This then makes the dorsal annulus redundant and allows it to protrude further dorsally into the vertebral canal. Similar considerations would apply to fenestration of type II thoracolumbar IVD. For this reason, fenestration cannot be advocated for prophylaxis of type II IVDH.

New Work in Development

Novel Approaches to Treatment of Acute SCI Resulting from IVDH

Neuroprotection. Neuroprotective treatments for SCI target acute and subacute secondary events, thereby mitigating the parenchymal damage that follows primary injury. Processes and pathways that therapies have targeted include inflammatory events, oxidative stress, excitotoxicity, intracellular calcium accumulation, blood–spinal cord barrier disruption, extracellular matrix derangement, caspase activation, and many others.[110] High-dose glucocorticoids were the first neuroprotective agents intensively studied in animal models and subjected to the clinical trial process in humans with SCI. Although data concerning the benefits of this approach in humans with SCI have been conflicting, these early trials and the subsequent controversy that ensued helped establish a framework by which candidate therapeutics should be studied. Currently, clinical trials in humans are under way investigating neuroprotective strategies such as riluzole, minocycline, BA-210 (a Rho antagonist), zoledronic acid, and therapeutic hypothermia.[111–113]

Very few neuroprotective clinical trials have been completed in dogs with IVDH. Study patients have varied with regard to the severity of SCI, timing of injury, outcome matrices, use of blinding and randomization, and the strength of supporting biological data. Polyethylene glycol (PEG) was studied in a small population of dogs with thoracolumbar IVDH that lacked pelvic limb deep nociception using an open-label design.[114] The biological basis for this study was animal model experiments showing electrophysiological recovery and parenchymal sparing after PEG delivery.[115–117] In dogs with IVDH, PEG administration was reported to enhance motor and sensory recovery from complete SCI compared with a noncontemporaneous historical control group.[114] Although these data were promising, the open-label design and use of control data from medical records are important limitations. A phase III study in dogs lacking deep pain sensation after thoracolumbar IVDH, examining the effect of PEG in comparison to MPSS and saline placebo has been completed recently by investigators at North Carolina State University, and the results should be reported soon.

A phase II, blinded, randomized study investigating *N*-acetylcysteine (NAC) was completed in dogs with thoracolumbar IVDH with and without pelvic limb deep pain sensation.[118] The biologic basis for this intervention was evidence of oxidative stress in dogs with IVDH,[119] the well-documented antioxidant properties of NAC,[120,121] and data in an animal model of spinal cord ischemia suggesting that NAC enhanced motor recovery.[122] The delivery of NAC to injured dogs did not improve motor recovery as measured by an abbreviated ordinal gait score. However, the limited nature of the gait scale, relatively small number of dogs included, and variable timing of SCI may have hindered detection of outcome differences between treatment groups.

Recently, a large-scale (>100 animals), randomized, blinded phase II study investigating a matrix metalloproteinase blocker in dogs with thoracolumbar IVDH was completed at Texas A&M University. The study rationale was based on animal model experiments demonstrating that MMP-9 expression contributed to lesion progression and that pharmacologic blockade of MMPs improved histologic and motor outcomes.[123] Additional supporting data included evidence from dogs with thoracolumbar IVDH that showed MMP-9 expression was associated with early, severe SCI.[124,125] Although trial results have not yet been published, a follow-up study focusing on this same neuroprotective approach has been funded by the US Department of Defense and recently has begun enrollment. The US Department of Defense has also sponsored an acute-phase study to evaluate

glial growth factor 2 at North Carolina State University, which will begin shortly.

Treatments for Long-Standing SCI. In the chronic stage after IVDH, the spinal cord has become irreversibly damaged, with loss of axons and neurons and normal tissue replacement by extensive gliosis. The reactive glial scar and production of proteoglycans prevents regeneration of damaged axons or sprouting of undamaged fibers across the lesion site.[126]

Although spontaneous plastic responses in the CNS can allow recovery of much lost function,[127] dogs with severe spinal cord injuries may be left with unsatisfactory function including loss of continence and inability to ambulate effectively. Similar results occur in some human patients and this has driven an intense search during the past 15 years for new therapies that can reverse this loss of function. Primarily, the aim is to promote regeneration of axons across the lesioned site, enhance plasticity, or both. Despite much laboratory work on these therapies, there have not yet been successful translations into human or veterinary medicine.

Therapies have been designed to promote axon regeneration center on altering the glial environment of the spinal cord so as to allow regrowth across the lesion site. This can be achieved in many ways, but the most frequently employed are cell transplants, including Schwann cells, olfactory ensheathing cells (OECs), and, more recently, various types of stem cell.[128] In laboratory experiments, many of these interventions have been shown to promote axon regeneration and recovery of lost function, but these gains have not translated into clinical success. A recent transplantation study, using OECs in chronically injured pet dogs, showed a benefit of transplantation, although the observed improved pelvic limb stepping was not accompanied by evidence of improved brain control over limb motion.[129]

Prognostic Indicators

From the owners' point of view, it would be very helpful if veterinarians were able to determine which dogs were likely to recover full function after acute SCI resulting from disk herniation. At present, testing deep pain sensation is the only method that is in common use and it is unsatisfactory because, although it is known that approximately 50% of deep pain-negative dogs will recover, it is not possible to identify which of them will recover when they present. The use of biomarkers to give further information has been explored in many studies. Notably, Witsberger et al[130] described the predictive value of myelin basic protein concentration and creatine kinase activity in CSF of paralyzed dogs, especially when combined with physical (ie, deep pain) testing.[131] Similarly, high levels of MMP-9 activity in CSF are also associated with poor recovery.[124,125] A recent study determining the concentration of tau protein in the CSF showed a positive association with the severity of spinal cord damage. A CSF tau concentration >41.3 pg/mL had a sensitivity of 86% and specificity of 83% to predict unsuccessful outcome in plegic dogs. CSF tau concentrations may therefore also serve as a prognostic indicator in dogs with IVDH.[132] Although these analyses may be of value in the future, the potential predictive value cannot be derived from one population sample alone (the predictive value depends on the prevalence of recovery or nonrecovery as well as the test itself) and will require validation in wider populations. Moreover, at present, these tests would not be appropriate for clinical use because of the delay between sample acquisition and the need for intervention, but similar variables may be developed in the future into ELISA tests that could be performed at the kennel side.

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