Urological Sequelae to Acute Spinal Cord Injury in Pet Dogs: A Natural Disease Model of Neuropathic Bladder Dysfunction

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The authors review urologic dysfunction, including urine retention, incontinence, and recurrent and resistant urinary tract infection, in dogs as a sequela to acute spinal cord injury. Urologic sequelae to acute spinal cord injury (SCI) pose significant complications in human and canine patients impacting quality of life and long-term cost of treatment. Dogs with intervertebral disc extrusion may serve as a natural disease model of acute SCI for investigating translational interventions, both prophylactic and therapeutic, for urologic dysfunction in human SCI patients. **Key words:** *dysuria, incontinence, intervertebral disc extrusion, urinary tract infection*

The study of naturally occurring disease in pet dogs has proven useful in understanding physiology and in developing and testing new treatments for an assortment of human conditions.[1-5] Naturally occurring traumatic spinal cord injury (SCI) is common within the general population of pet dogs, where approximately 20,000 new cases are managed by veterinary neurologists and spinal surgeons each year in the Unites States alone. We manage approximately 150 cases per year at Ohio State University Veterinary Medical Center.[6] In contrast to what is observed in people, the majority of SCI in dogs is caused by acute intervertebral disc extrusions (IVDE), with lesser numbers caused by traumatic injury leading to fracture/luxation, such as falls, being hit by a motor vehicle, or other. Despite the difference in underlying etiology, acute IVDE results in a mix of compressive and concussive forces that parallel those observed in most human SCIs. Given the high prevalence of this form of SCI in dogs, recent attention has focused on the use of this veterinary patient population as a translational model through which to study new interventions and document the magnitude of treatment effect for new therapies that may improve outcomes for people living with SCI.[6-8]

Although not a replacement for experimental models, this canine model of SCI may address some of the factors identified by clinicians and neuroscience researchers as barriers to translational success in the field, including lack of genetic diversity and comorbid conditions in experimental models, homogeneity of experimentally induced injuries, and issues with size and complexity of the rodent spinal cord relative to humans.[9-11] Important attributes of the canine model can be used to augment information gained from the laboratory setting: (a) naturally occurring injury can be studied in a clinical population of dogs with diverse genetic backgrounds that receive advanced imaging, surgery, and postoperative care similar to that of people with SCI; (b) physical size of the canine central nervous system and metabolism in the dog allow for ease in "scaling up" of therapeutics for human trials; (c) dogs with severe SCI that do not recover are often managed as chronic paraplegics by their owners, which offers a valuable model of chronic injury that can be difficult to reproduce in the experimental setting; and (d) outcome measures used in canine SCI clinical trials mirror those used in human clinical trial settings, including a host of locomotor scales, quantitative sensory testing techniques, measures of spasticity, and urodynamic studies. This ensures that observed improvements are relevant to the human condition.

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Background and Clinical Signs

SCI in pet dogs is most common in the thoracolumbar spine and is caused by several underlying etiologies including spinal fracture, ischemic injury, and IVDE; however, IVDE is by far the most common cause of acute SCI in dogs, accounting for as much as 90% of the injuries. Most IVDE occurs between the T11 and L3 vertebral levels.[12,13] It should be noted that dogs have 13 thoracic and 7 lumbar vertebrae, with the spinal cord persisting within the vertebral canal to the level of the L6 vertebral body; therefore most thoracolumbar IVDE-associated SCI in dogs are equivalent to a mid-thoracic injury in a person. IVDE-associated SCI can occur in any breed of dog but is most common in chondrodystrophic breeds including Dachshund, Pekingese, Beagle, Lhasa Apso, Shih Tzu, Miniature Poodle, Maltese and Bichon Frise, and American Cocker Spaniel.[14-18] In these dogs, IVDE most commonly occurs secondary to chondroid disc degeneration. This degenerative process begins early in life, for example, as early as 2 months of age in Dachshunds.[19-22] Initially mesenchymal cells of the nucleus pulposus are replaced with chondrocyte-type cells. A loss of glycosaminoglycans, increase in collagen, and decrease in water content are progressive, and the normally gelatinous nucleus pulposus is transformed to hyaline cartilage leading to loss of normal hydroelastic properties of the disc. In chondrodystrophic breeds, 75% to 90% of the nucleus pulposus is transformed to hyaline cartilage by 1 year of age. In contrast, Greyhounds, and presumably other non-chondrodystrophic breeds, maintain the gelatinous nature of their nucleus pulposi into old age.[23-26] The degenerated disc is unable to withstand normal forces, which makes them more prone to acute, high-velocity extrusion of nucleus pulposus under relatively normal exertions.[14,22,24,27] This results in a sudden onset mixed compressive and contusive injury to the spinal cord.

Clinical Assessment of Dogs With SCI

Routine clinical evaluation of the veterinary patient with SCI occurs by way of a complete neurologic examination performed by the veterinary clinician. Many dogs with acute injuries are referred to tertiary care facilities, where their evaluation and care are provided by a board-certified veterinary neurologist or trained spinal surgeon. Typical components of the canine neurological examination include evaluation of gait using open-field testing, assessment of cranial nerves and spinal reflexes, documentation of behavioral responses to a noxious stimulus applied to the digits as a surrogate marker of nociceptive processing, and observational assessment of bladder voiding. Additional and more in-depth locomotor, sensory, and urologic assessments are well described in the literature and may also be performed, particularly as part of veterinary SCI clinical trials.[28-35]

Neurologic abnormalities observed in dogs with IVDE-associated SCI range from spinal pain with or without mild neurologic deficits to loss of motor and sensory function caudal to the injury site (American Spinal Injury Impairment Scale [AIS] A equivalent injury).[14-18] Severe injuries may lead to sensorimotor complete lesions and generally result from a mixed compressive and contusive injury to the spinal cord consisting of variable degrees of gliosis, hemorrhage, myelomalacia, demyelination, microglial activation, and eventual formation of glial scar.[36-39] Severity of neurologic signs correlates with severity of histologic injury grade in most cases, and sensorimotor complete (AIS A equivalent) injuries account for approximately 15% of the IVDE-associated SCIs in dogs.[13,39,40] In addition to changes in motor and sensory function, urinary dysfunction is also common after IVDE-associated SCI, particularly when there are severe motor deficits or when lesions affect the pelvic intumescence or cauda equina.[16,18] Spinal shock, although observed in dogs with acute SCI, is a relatively short-lived phenomenon in dogs compared to other species. The time course for recovery from spinal shock has been carefully described in a few veterinary papers; these accounts and our experience suggest that reflexes associated with the sacral segments return very rapidly (within hours), whereas absence of the patellar reflex and reduced pelvic limb muscle tone may remain for 24 to 48 hours after injury.[41] In combination with neurologic examination findings, specific localization of the injury site is further documented with advanced

imaging (computed tomography or magnetic resonance imaging), and compressive lesions are frequently treated with surgical decompression via laminectomy.

Urologic Consequences of IVDE-Associated SCI

Similar to what is observed in humans, severe SCI in pet dogs leads to dysfunction in urine voiding and storage and impacts quality of life[42,43] and long-term survival.[44] Dogs with substantially reduced or absent motor function related to a lesion above the level of the sacral segments develop upper motor neuron (UMN) bladder dysfunction resulting in urinary retention and intermittent overflow incontinence. In a normal dog, the pontine micturition center in the brainstem is the UMN control for normal urination. The cerebral cortex can override this brainstem control to a certain degree to allow for voluntary urination, but cortical control is not necessary for urination to occur. In contrast, pontine micturition center communication with the pelvic nerve via spinal UMN tracts (spinothalamic pathways, reticulospinal tracts, tectospinal tracts) is necessary in order to initiate urination by detrusor muscle contraction. This process is called the *detrusor reflex* (**Figure 1**). If a UMN SCI is severe enough to block these spinal tracts, this communication cannot occur and the detrusor reflex fails to initiate. UMN bladders typically feel turgid on palpation, and the urethral sphincter maintains normal to increased muscle tone, which makes manual expression difficult.[17,45] Typically UMN bladder dysfunction carries a good prognosis for recovery in dogs that recover the ability to walk. Prognosis for recovery of ambulation and urination from acute thoracolumbar IVDE in dogs is good to excellent (reported range, 80%-95%) with surgery as long as nociception to the pelvic limbs is intact. If nociception is absent to the pelvic limbs, prognosis for recovery of ambulation, and therefore urinary function, is more guarded (approximately 50%) with surgery.[15,16,45,46] Usually voluntary urination returns around the time pelvic limb motor function returns.

In dogs, the pelvic nerve allows contraction of the detrusor muscle of the bladder wall via parasympathetic innervation. This nerve comes from the S1-3 spinal cord segments (**Figure 1**). SCI affecting these segments or the sacral nerve roots of the cauda equina leads to dysfunction of the pelvic nerve directly. In this case, a lower motor neuron (LMN) bladder may be seen. When the pelvic nerve is impaired, the detrusor muscle has poor tone and cannot contract. The bladder feels flaccid on palpation; because the pudendal nerve is often concurrently affected, urethral sphincter tone is also reduced. Affected dogs cannot urinate and have constant overflow incontinence.[17,45-47] LMN bladder dysfunction carries a more guarded prognosis for recovery than UMN bladder dysfunction. This prognosis may be better with more acute SCIs such as those that occur with acute IVDE than with chronic injury. In the veterinary literature, there is more information regarding prognosis for LMN bladder dysfunction with chronic diseases such as degenerative lumbosacral stenosis (DLS), because this is a more common cause of LMN bladder dysfunction in dogs. In these reports, recovery of continence occurred in 55% to 87% of cases following surgery.[15,45,48] In one report of 61 dogs with acute lumbosacral SCI, most due to IVDE, 64% regained urinary continence.[49]

Bladder Management in Dogs with SCI

UMN and LMN bladder dysfunction must be managed with manual expression or urinary catheterization, either intermittent or indwelling, for as long as urinary retention is present. For dogs with severe SCIs, this can mean lifelong bladder management.[47] In dogs, manual bladder expression is usually attempted first and can be an effective way to manage urine retention, particularly in smaller dogs. Clients can be taught to manage their dog's bladder at home in this way. However, this method can be challenging in UMN bladder dysfunction due to increased urethral sphincter tone. Bladder evacuation is often incomplete, and dogs may become sore due to pressure on abdominal muscles. It is also time consuming, requiring 3 to 16 hours per week.[46] Clients may mistake overflow incontinence for voluntary urination and therefore stop bladder expression prematurely. There is also a small risk of injury to the bladder with excessive force. Medical therapy can help with bladder expression or voluntary urination in some

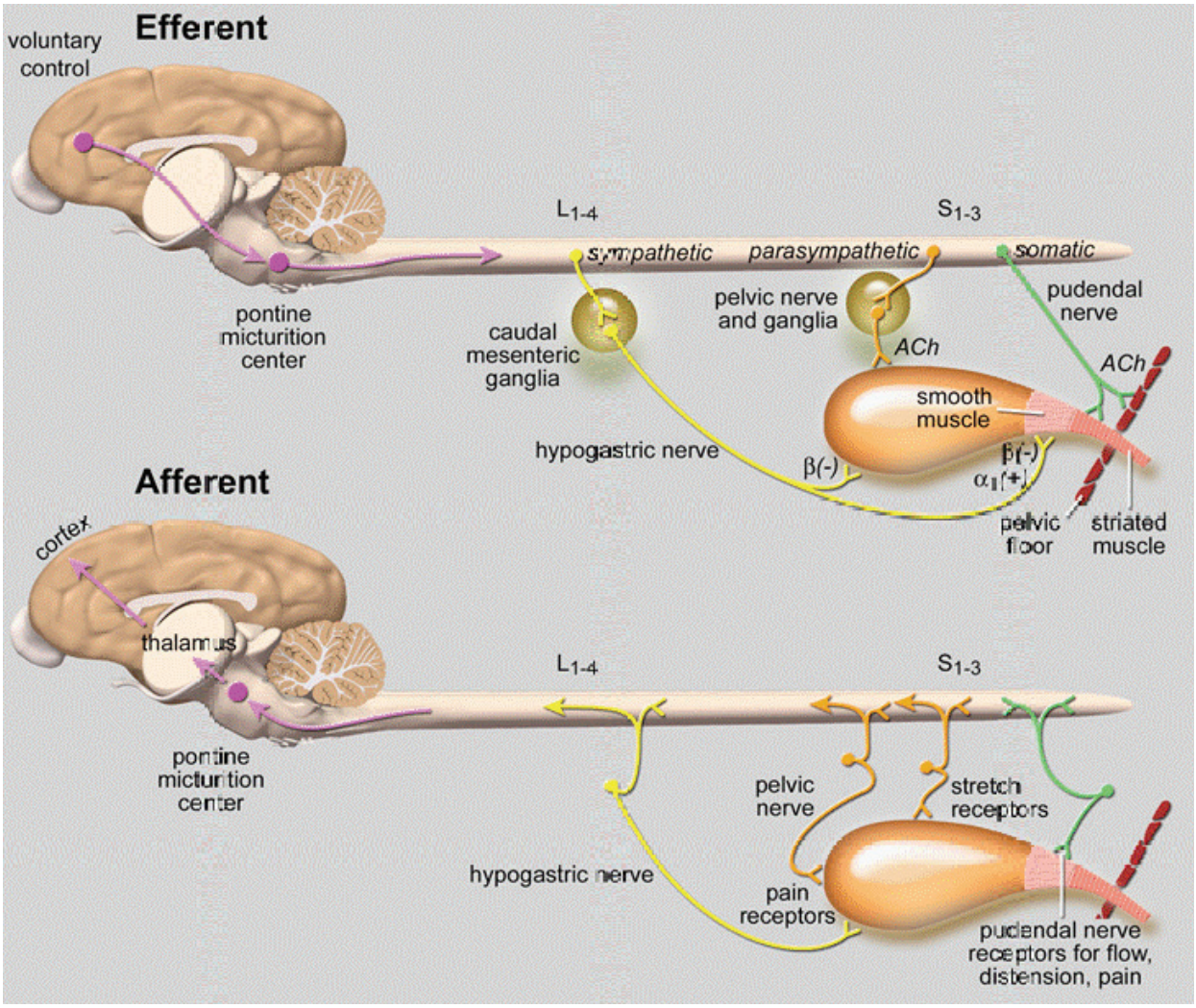

Figure 1. Neurophysiology of normal urination. Normal urination is controlled by components of the central and peripheral nervous systems. The sympathetic nervous system facilitates urinary bladder filling via the hypogastric nerve from the L1-4 spinal cord segments. The hypogastric nerve causes contraction of the internal urethral sphincter via $\alpha 1$ receptors and relaxation of the bladder wall via β receptors in the detrusor muscle allowing the bladder to fill. The parasympathetic nervous system facilitates urinary bladder voiding via the pelvic nerve from the S1-3 spinal cord segments that synapses on cholinergic receptors in the detrusor muscle. The pudendal nerve is a somatic nerve that is under conscious control causing contraction of the external urethral sphincter. The pontine micturition center in the brainstem facilitates the filling and voiding phases. The pontine micturition center must signal the pelvic nerve in order to initiate voiding. If this signal is blocked, such as with an UMN spinal cord injury, voiding cannot be initiated. The cerebral cortex can consciously inhibit the pontine micturition center to allow for conscious voiding. However, cortical control is not necessary for voiding to occur. The urinary bladder spends the majority of time in the filling phase. There are stretch receptors in the detrusor muscle of the bladder wall. When the urinary bladder fills to a point that those stretch receptors reach threshold, afferent signals are relayed up the pelvic nerve and up the spinal cord afferent tracts to the pontine micturition center signaling the end of the filling phase. The pontine micturition center sends efferent signals down the spinal cord efferent tracts inhibiting the hypogastric nerve and facilitating the pelvic nerve. The internal urethral sphincter relaxes, the detrusor muscle contracts, and voiding is initiated. Reprinted, with permission, from Dewey CW, da Costa RC. *Practical Guide to Canine and Feline Neurology.* 3rd ed. Hoboken, NJ: Wiley-Blackwell; 2016.

cases. α-Sympatholytic agents such as prazosin, alfuzosin, tamsulosin, and phenoxybenzamine can facilitate relaxation of the internal urethral sphincter, making bladder expression easier. Skeletal muscle relaxants such as diazepam, dantrolene, and baclofen may help the external urethral sphincter relax, which also facilitates manual bladder expression. Parasympathomimetic medications (bethanechol and carbachol) can facilitate detrusor muscle tone in LMN or atonic bladders. There is little data supporting efficacy of these medications in veterinary patients.[47] Sacral cranial root stimulation (SARS) is an established treatment for human patients with detrusor overactivity and detrusor-sphincter dyssynergia; this treatment showed a voiding efficiency of >90% in 8 of 9 dogs tested.[29,47]

Indwelling catheterization is an effective means for keeping bladders evacuated; however, it is usually not recommended for dogs being sent home as owners may fail to recognize a catheter blockage. Catheters can also be inadvertently pulled out, risking urethral injury. Intermittent catheterization can be useful in male dogs, and some owners can be taught to do this at home. It is much more challenging in female dogs and often requires sedation, which precludes its use for female dogs in a home environment.[18]

Sequelae to urinary retention and overflow incontinence in dogs include recurrent urinary tract infections (UTIs),[17,18,46,50-54] pyelonephritis,[47] and urine scald.[46] This increased risk of UTI is due to an inability to clear bacteriuria due to urine retention, high residual urine volumes in the bladder, and increased exposure to uropathogens due to frequent urinary catheterization.[47,54]

Prevalence of UTI in dogs with acute IVDE has been reported to be as high as 38% within 6 weeks of surgery and as high as 52% in dogs with indwelling urinary catheters.[51,52] Dogs with more severe preoperative neurologic deficits that took longer to regain ambulation and voluntary urinary function are at greater risk for UTIs through the postoperative period.[50] Other risk factors include female sex, duration of indwelling catheterization, lack of perioperative antibiotics, lower intraoperative temperature, antibiotic administration during urinary catheterization, and administration of dexamethasone less than 48 hours prior to surgery.[51,53-55] One study showed an increase in risk of UTI by 20% per year increase in age, 27% for each day increase in duration of catheterization, and 454% with antimicrobial administration during catheterization.[54] Frequency of UTI was higher for dogs with indwelling catheterization than control dogs but was not higher than in dogs managed by manual expression.[18] One study looked at perioperative treatment with cefovecin versus cefazolin, and neither were protective against UTI in the population of dogs studied.[50]

Urinary tract isolates include enteric *Escherichia coli*,[47,56] *Enterococcus spp., Streptococcus spp., and Staphylococcus spp*.[47,50,56] Uropathogens can develop multidrug resistance following antibiotic exposure, and more than 30% of dogs with complicated UTIs have multidrug-resistant infections.[47] In dogs with long-term bladder dysfunction, repeated exposure to antibiotics due to recurrent UTIs can exacerbate uropathogen resistance. Urine culture and sensitivity should always be performed for this reason. Urine pH can influence the efficacy of antibiotics. For example, fluoroquinolones and aminoglycosides work best in an alkaline pH whereas β-lactams and tetracyclines work better in acidic pH. Some drugs are pH independent, such as clindamycin, amoxicillin, and clavulanate. Dietary or pharmacologic urine pH manipulation could be considered. Continued exposure to gut organisms or repopulation by a persistent infection that was incompletely cleared are common causes of recurrent UTI.[47]

Preventive strategies may include good hygiene to reduce gut pathogen exposure and assisted bladder voiding to eliminate bacteriuria and bacterial adhesion. Completeness of bladder emptying can be assessed by manual palpation or by measuring residual urine volume. Normal residual volume in dogs is estimated to be 0.2 to 0.4 mL/kg.[47] Prophylactics such as urine acidifiers (ammonium chloride) and urine antiseptics (nitrofurantoin, methenamine hippurate, and methenamine mandelate) may inhibit bacterial colonization.[47] The effect of cranberry extract on preventing UTI was evaluated in a small group of dogs and did not show any effect at the dosage used in that group. However, dogs with higher urine antiadhesion activity were less likely to have a UTI.[57]

IVDE-Associated SCI as a Model for Neuropathic Bladder Conditions

Numerous studies have evaluated novel therapeutics for SCI using the canine clinical model, and recent work by veterinary neurologists has aimed to formalize a clinical trial infrastructure for robust and efficient use of this model for translational therapeutic development.[9] Interventions have ranged from acute neuroprotective strategies to cell-based therapies and to treatments targeting the chronic SCI state.[33,47,58,59] Given the high prevalence of thoracolumbar lesions in dogs, suprasacral injuries are most common, and urodynamic assessment of these UMN lesions has been the focus of most of the reported veterinary clinical data.[60-65] Cystometric characteristics of neurogenic bladder dysfunction in dogs with SCI are similar to those of spinal cord-injured people and consist of reduced cystometric bladder capacity, abnormally low compliance, and involuntary detrusor contractions.[66-68] These similarities suggest that dogs with SCI may be a suitable model for human SCI-associated neuropathic bladder. In fact, several studies have used dogs with clinical SCI as a model through which to evaluate novel drugs or devices aimed at improving urologic outcome after SCI.

Of particular note, a recent study evaluated the effect of early blockade of matrix metalloproteinases (MMP) using a novel therapeutic (GM6001) on bladder function in dogs with IVDE-associated SCI via a randomized, controlled, double-blind veterinary clinical trial designed using CONSORT standards. The investigators evaluated the effect of a novel therapeutic, in combination with standard spinal decompression, in dogs with severe acute SCI and evaluated cystometric parameters at initial presentation and at 3, 7, and 42 days after injury. Results of the study suggest that dogs receiving the novel MMP inhibitor had higher bladder compliance at day 42 compared to those receiving the vehicle control whereas residual urine volume did not differ between groups.[69] The investigators suggest that GM6001 may be useful for improving bladder compliance after SCI. Because reduced bladder compliance is associated with an increased risk of UTI, they suggest that the drug may represent a potential strategy for mitigating this important complication of SCI in people.[70] This study serves as an important proof of concept for the feasibility of evaluating novel therapeutics targeted at urological outcomes in a clinical population of pet dogs with SCI, paving the way for future translational studies with similar intent. The recent work by Granger et al evaluating an implantable sacral stimulator device in dogs further supports the feasibility of the model for novel device evaluation as well.[30]

Conclusion

Urological consequences of SCI are a major complication in human and canine patients. Urinary retention, incontinence, and recurrent and resistant UTI impact quality of life and costs associated with long-term management. Dogs represent an important natural disease model through which to study translational treatments and prophylactic strategies to improve urologic outcomes after SCI. Attributes such as the high prevalence of injury in the pet dog population, similarities in urologic alternations between dogs and people, and the clinical nature of the injury support the use of pet dogs with SCI as a complimentary model system to further evaluate therapies that have shown promise in laboratory models of SCI.

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