The Veterinary Journal 237 (2018) 49–54

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Original Article

Somatosensory and motor evoked potentials in dogs with chronic severe thoracolumbar spinal cord injury

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ARTICLE INFO

Article history:
Accepted 21 May 2018

Keywords:
Canine
Electrophysiology
Physical therapy
Recovery
Spinal walking

ABSTRACT

Some dogs that become paraplegic after severe spinal cord injury regain ambulation on the pelvic limbs despite permanent loss of pelvic limb sensation, a phenomenon termed 'spinal walking'. Plastic changes in spinal cord circuitry are thought to mediate this form of recovery but the precise circumstances that favor its development are not known. More information on this phenomenon would be helpful because it might be possible to coax more function in chronically paraplegic animals so improving their, and their owners', quality of life. We analysed the correlation of 'spinal walking' and pelvic limb pain sensation with recordings of scalp and spinal somatosensory and transcranial magnetic motor evoked potentials. We prospectively examined 94 paraplegic dogs (including 53 Dachshunds) that had sustained T10 to L3 spinal cord injury (including 78 dogs with acute intervertebral disc herniation) at a median time of 12.0 months from injury.

Nine dogs exhibited 'spinal walking' and nine other individuals had intact pelvic limb pain sensation. Of 34 tested, 12 dogs had recordable scalp somatosensory evoked potentials. Fifty-three of 59 tested dogs had recordable spinal somatosensory evoked potentials, but only six had recordable potentials cranial to the lesion. Twenty-two of 94 tested dogs had recordable transcranial magnetic motor evoked potentials in the pelvic limb(s). There was no apparent association between intact evoked potential recording and either spinal walking or intact pain sensation. We conclude that factors other than influence, or lack of influence, of input carried by spinal cord long tracts mediate recovery of spinal walking.

Introduction

Spinal cord injury is common in pet dogs, mainly resulting from intervertebral disc herniation, fractures and vascular lesions (Moore et al., 2017). A small proportion of dogs, estimated to be approximately 16% of cases presented with acute intervertebral disc herniation (Granger and Carwardine, 2014), become paraplegic and lose sensation in the hindquarters. Of these, between 20 to 40% remain permanently unable to walk and, usually, also unable to control urination and defecation (Scott and McKee, 1999; Olby et al., 2003; Ito et al., 2005; Jeffery et al., 2016). Not only is more information required to aid owners in providing optimal care but these chronically-injured dogs have many similarities to chronically-injured humans and so constitute a model in which novel therapies can be tested. Data on baseline function may also aid stratification of participants in future human or veterinary clinical trials.

One intriguing aspect of chronic spinal cord injured dogs is that some develop so-called 'spinal walking' in which they regain ambulation, despite absence of recovery of sensation in the pelvic limbs. In experimental dogs, it has been established that pelvic limbs can generate a gait pattern that allows locomotion despite complete thoracolumbar spinal cord transection (Handa et al., 1986). Because it is rarely possible to ascertain whether the spinal cord is truly transected in clinical injuries, spinal walking in these individuals is defined by the loss of 'deep pain perception' in association with the ability to walk for a potentially unlimited period and the ability to regain a standing posture from recumbency (Gallucci et al., 2017).

At present it is uncertain what factors are important in promoting development of spinal walking. It is known that most dogs with experimental transection of the spinal cord can acquire this activity, although it may be considerably delayed from the

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https://doi.org/10.1016/j.tvjl.2018.05.007
1090-0233/

time of injury (Handa et al., 1986). In clinical cases, the extent of injury to the spinal cord is rarely known and so there is an uncertain relationship between severity of injury and development of spinal walking. A recent analysis suggested that spinal walking is associated with intact conduction through the descending motor tracts, as assessed by transcranial magnetic motor evoked potential (TMMEP) recordings (Lewis et al., 2017).

In the course of carrying out two randomized controlled trials on novel therapies for chronic spinal cord injury in pet dogs (Granger et al., 2012; Hu et al., 2018), we have acquired plentiful baseline data from which we can examine various hypotheses regarding the relationships between spinal walking and spinal 'long tract' conduction. Spinal walking is thought to be a consequence of increased activity in the segmental reflex pathways within the pelvic limb central pattern generator (Pearson, 2000; Raineteau and Schwab, 2001), implying that any residual input from descending tracts might make it less likely for spinal walking to occur. Therefore, we hypothesized that (1) spinal walking would be associated with failure to record TMMEPs in the pelvic limbs. Second (2), because both somatosensory evoked (SEP) and TMMEPs imply conduction through the spinal cord, we considered that dogs with pain perception would be more likely to have TMMEPs recordable from their pelvic limbs or SEPs recordable over the brain or spinal cord. Lastly (3), we thought that dogs with evidence of longer regions of spinal cord loss would be more likely to exhibit spinal walking (because, as a corollary of hypothesis 1, they would less likely have interference of descending influence on pattern generators controlling pelvic limb movements).

Materials and methods

Dogs

Participants were pet dogs that had been prospectively enrolled with owner consent into one of two clinical trials of novel therapy for chronic severe spinal cord injury. In both trials, dogs had to fulfill the same inclusion criteria: (1) weight <25 kg; (2) had sustained acute, traumatic T10 – L3 spinal cord segment injury; (3) otherwise healthy; and, (4) had failed to regain either 'voluntary ambulation', pain sensation, or both, in their pelvic limbs by at least 12 weeks after injury. 'Voluntary ambulation' was defined as being able to walk 10 consecutive steps unaided *plus* having evidence of pain perception in the pelvic limbs. However, dogs with some ambulatory ability – as defined in the clinical assessment section below – were not excluded from these trials, so long as they *did not* show evidence of conscious pain perception in the pelvic limbs. For inclusion, on pre-enrolment examination, each dog also had to have intact pelvic limb reflexes and normal range of motion in the pelvic limb joints when manipulated. The location of the lesion in each dog was known from neurological examination, imaging studies and surgical reports at entry to the study. The location was stated as the intervertebral disc space forming the epicenter of the lesion, based on imaging and surgical findings (*i.e.* attributed to one spinal cord segment between T10 and L3), although the histopathological spinal cord lesion would, in most cases, have extended further cranially and caudally along several spinal cord segments.

The data described here were acquired from enrolled dogs *before* they underwent any of the planned interventions examined in Studies 1 and 2.

Clinical assessment

Dogs were categorized according to whether they: (1) could ambulate on the pelvic limbs without support; and, (2) exhibited evidence of conscious perception of stimuli applied to the pelvic limbs or tail, up to and including intensely noxious pressure applied by pliers to the digits and tail. To be considered 'ambulatory' a dog had to be able to walk 10 consecutive unaided steps on a concrete floor without falling or the lateral aspect of any part of the foot or metatarsals touching the ground. Each dog that was able to ambulate in this way also had to have no evidence of pain perception in the pelvic limbs or tail and was therefore referred to as a 'spinal walker'. It was also recorded whether dogs could walk between 1 and (no more than) 10 steps, or if they had some pelvic limb movement but no ability to walk, or if they showed no pelvic limb movement at all. 'Deep pain' response was considered intact if the animal consistently vocalized, turned the head to the source of the stimulus, or attempted to bite, in response to stimuli applied to the pelvic limb digits or tail.

Electrodiagnostic procedures were performed under sedation with 0.005 mg/kg dexmedetomidine (Zoetis) IV and 0.2 mg/kg butorphanol (Zoetis) IV. During the procedure, each dog was placed in sternal recumbency and routinely monitored until the end of the procedure, when 0.05 mg/kg atipamezole (Zoetis) was given IM to reverse dexmedetomidine and the dog was fully conscious and recovered their normal mobility. Brief information on recording methods are included below; additional detail is available in Appendix: Supplementary material.

Somatosensory evoked potentials

Somatosensory evoked potentials were recorded from the sensory cortex or vertebral column using standard methods (Poncelet et al., 1993). In both studies, each tibial nerve immediately proximal to the hock joint was stimulated individually with a subcutaneous electrode using just sufficient intensity to elicit a minimally perceptible movement in the pelvic limb digits (*i.e.* just above motor threshold). Repetitive, rectangular impulses of 0.2 ms duration were then applied to the nerve at a frequency of 3.1 Hz and intensities varying from 0.2 to 1 mA.

For spinal SEP recordings, the reference monopolar electrode was placed in the epaxial muscle 1 cm lateral to the recording electrode placed on the vertebral lamina ipsilateral to the tibial nerve stimulation. Recordings were commenced on each side at the cranial aspect of L6 and progressed cranially in steps of one vertebra until potentials could no longer be recorded; location, amplitude and latency of the potential at the cranial-most vertebra on each side were recorded for analysis (Fig. 1). We used the location of the most cranial recording site to calculate the number of spinal cord segments from that segment to the lesion epicenter (*i.e.* number of spinal cord segments 'below' the lesion). If recordings could be obtained above the lesion epicenter, we then calculated the number of spinal cord segments between the lesion epicenter and the most cranial recording (*i.e.* number of spinal cord segments 'above' the lesion), providing information on conduction across the

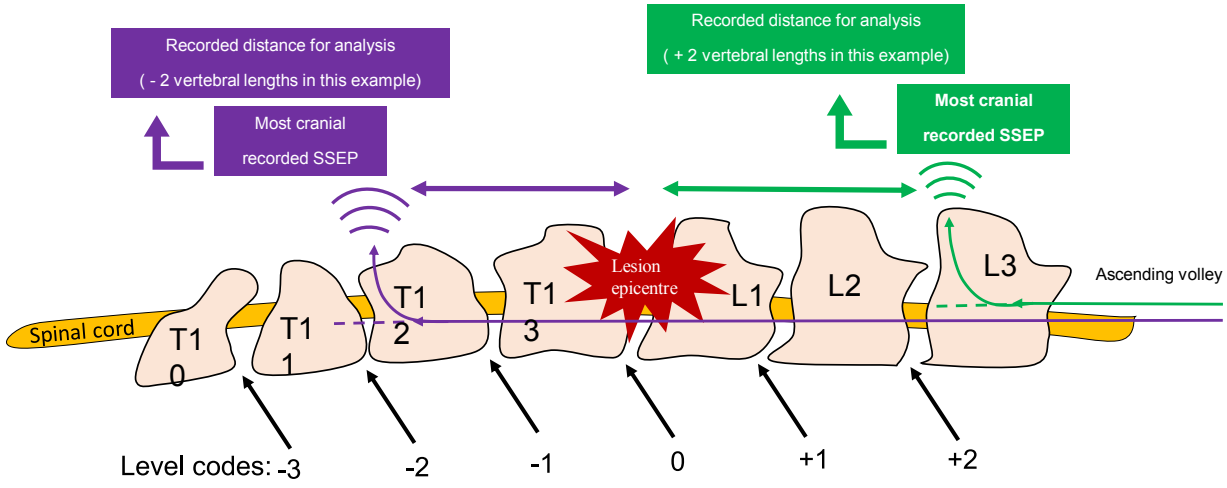

Fig. 1. Schematic diagram depicting measurement of distance between cranial-most site of somatosensory evoked potential recording and lesion epicenter site. Measurements were made in units of one vertebra, with each vertebral space allocated a code starting from T13-L1 = 0, corresponding to the sites at which consecutive recordings were attempted. SSEP — somatosensory evoked potential.