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The prognostic value of cerebrospinal fluid characteristics in dogs without deep pain perception due to thoracolumbar disc herniation

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ABSTRACT

Providing a pre-operative prognosis for dogs presented with absent deep pain perception (DPP) is extremely challenging, as the overall recovery rates widely vary. This study assesses the possible correlation between the severity of spinal cord injury and CSF cytology in 31 paraplegic dogs presented with absent DPP due to acute thoracolumbar intervertebral disc herniation (TL-IVDH). All dogs underwent surgical decompression immediately following diagnosis. CSF TNCC, macrophage percentage and macrophage to monocyte (MΦ:M) ratio were significantly higher in dogs that failed to regain DPP within 10 days post-operatively and in dogs that failed to regain ambulation at the end of the study period ($P < 0.05$). MΦ:M of 0.73 and higher corresponded to a sensitivity of 54% and specificity of 100% for prediction of a negative long-term outcome. CSF TNCC, macrophage percentage and MΦ:M ratio effectively predicted regaining DPP and the long-term outcome in dogs that lost DPP due to acute TL-IVDH.

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1. Introduction

Thoracolumbar intervertebral disc herniation (TL-IVDH) is a common spinal cord disorder in dogs (De Lahunta and Glass, 2009; Dewey, 2008). The severity of the clinical signs may vary and severely affected dogs might present paraplegia and absent deep pain perception (DPP) (De Lahunta and Glass, 2009; Dewey, 2008; Laitinen and Puerto, 2005; Ruddle et al., 2006). While dogs presented with intact DPP are likely to regain ambulation following conservative or surgical treatment (Coates, 2000; Davis and Brown, 2002; Ruddle et al., 2006; Sharp and Wheeler, 2005), loss of DPP is commonly associated with guarded or poor prognosis, particularly when DPP was absent for over 48 h pre-operatively (Griffiths, 1982; Jeffery, 1995). A significantly higher neurologic recovery rate was recorded in dogs that regain DPP within 2 weeks after surgery, when compared to dogs in which DPP remained absent, hence making the recovery of DPP within 2 weeks post-operatively a useful prognostic tool for the overall neurologic recovery (Laitinen and Puerto, 2005). Nevertheless, the recovery rates in such cases still vary considerably, ranging between 0% and 76% (Anderson et al., 1991; Coates, 2000; Duval et al., 1996; Ruddle et al., 2006; Schulman and Lippincott, 1987; Scott and McKee, 1999). For this reason, more accurate, pre-operative prognostic indicators are needed in such dogs.

Various prognostic indicators for functional recovery in dogs with TL-IVDH have been previously suggested including severity, duration and rate of progression of clinical signs and extent of spinal cord contusion and compression (Bohn et al., 2006; Davis and Brown, 2002; Duval et al., 1996; Laitinen and Puerto, 2005; Olby et al., 2003; Ruddle et al., 2006; Tarlov and Klinger, 1954). High serum concentrations of glial fibrillary acidic protein (GFAP) (Sato et al., 2013) and phosphorylated neurofilaments (Nishida et al., 2014) were suggested as pre-operative indicators of a negative outcome in dogs with TL-IVDH. In addition, several imaging features were also proposed as pre-operative indicators of a negative outcome, including extensive contrast column attenuation upon a myelogram and intramedullary T2-weighted hyperintensity, observed on magnetic

Abbreviations: AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; DPP, deep pain perception; MΦ:M, macrophage to monocyte ratio; ROC, receiver operator characteristics; TNCC, total nucleated cell count; TL-IVDH, thoracolumbar intervertebral disc herniation

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resonance imaging (Duval et al., 1996; Ito et al., 2005; Penning et al., 2006). Moreover, intra-operative evidence of intramedullary hemorrhage or myelomalacia are interpreted as poor prognostic indicators and serve as additional means of predicting the clinical outcome in dogs presented with absent DPP (Duval et al., 1996; Schulman and Lippincott, 1987; Scott and McKee, 1999).

Cerebrospinal fluid (CSF) analysis characteristics were also proposed as a potential pre-operative indicators of the severity of spinal cord injury (Levine et al., 2010, 2014; Roerig et al., 2013; Srugo et al., 2011; Windsor et al., 2008). High CSF Tau protein (Roerig et al., 2013) and myelin basic protein (Levine et al., 2010) concentrations were previously suggested as indicators of a negative outcome in dogs with TL-IVDH. In addition, in our previous work on non-ambulatory paraparetic and paraplegic dogs (Srugo et al., 2011), CSF pleocytosis, high percentage of macrophages and macrophage to monocyte (MΦ:M) ratio were positively associated with the severity of clinical signs at presentation and with the outcome.

The present study further assesses whether the same CSF parameters may be used to predict functional recovery in dogs that lost DPP due to acute TL-IVDH. Attending clinicians are often faced with the need to provide a pre-operative prognosis for functional recovery in such paraplegic dogs. Providing prognosis in dogs presented with absent DPP is more challenging, as the overall recovery rates widely vary and if given poor prognosis may lead to euthanasia.

2. Materials and methods

2.1. Study design and animals

Medical records were retrospectively reviewed for paraplegic dogs with absent DPP due to acute TL-IVDH. Dogs were included in the study if they were presented within 48 h from the occurrence of the non-ambulatory state, if a surgical confirmation of acute TL-IVDH was established, if CSF, obtained through cerebromedullary cistern puncture, was analyzed pre-operatively and if surgical decompression was performed immediately following the diagnosis. Dogs were excluded if signs of other concurrent neurologic disorders were present, or if CSF samples were assessed to be iatrogenically blood contaminated, based on a combination of >500 red blood cells (RBC)/μl and absence of erythrophagia (Adams, 1982; Chrisman, 1992).

All diagnostic tests and therapeutic interventions were conducted as part of the routine treatment of dogs with TL-IVDH and performed with their owners consent. No experimental measures were conducted in this study.

Data collected from the medical records included the signalment, the time lag from occurrence of the non-ambulatory state to presentation, prior glucocorticoid administration, cerebellomedullary CSF analysis findings and time lags from surgical decompression to regaining DPP and ambulation. Short-term (30-day, obtained from the medical record) and long-term (>30-days, obtained from the medical record and through telephone interviews with owners) post-operative follow-up evaluations were recorded. Surviving dogs were followed until ambulation was regained, or for at least 3 months (range, 3–24) post-operatively.

Neurologic examinations were conducted at presentation and on days 1, 2, 10 and 30 post-operatively by a board certified neurologist or neurology residents. The time at which DPP was lost was defined as the time when the owners first noticed the loss of ambulation in their dog. At each post-operative neurologic evaluation, dogs were assigned a grade based on severity of neurologic dysfunction (using a 0–6 scale; 0, normal; 1, spinal hyperesthesia; 2, conscious proprioceptive deficit or ambulatory paraparesis; 3, non-ambulatory paraparesis; 4, paraplegia; 5 paraplegia with urinary or fecal incontinence; and 6, paraplegia with absent DPP). DPP was evaluated by applying a gradually increasing noxious stimulus using hemostatic forceps to each digit of both pelvic limbs and the tail.

The final outcome was considered successful when dogs regained ambulation and complete control of micturition, even if mild ataxia or proprioceptive deficits were still apparent. Regaining DPP was considered favorable intermediate phase toward recovery and was statistically analyzed separately from the final outcome.

2.2. CSF collection and analysis

Cerebellomedullary CSF samples were collected using hypodermal 1.5 inch, 21G needles into two sterile glass red-top tubes and analyzed within 20 min of collection. Total cell count was determined using a hemocytometer by counting all cells (nucleated cells and RBCs) within 10 large squares of the grid (Wamsley and Alleman, 2004). Two 200-μl aliquots (one from each tube) were cytocentrifuged (Shandon cytospin 4, Thermo-Sheldon Electron Corporation, Pittsburgh, PA; at 800 rpm, 72 *g* for 10 min) and slides (Cytoslide, Pittsburgh, PA) were stained; one with modified Wright's stain (Hema-Tek 2000 slide stainer, model 4488B; stain: Hematek stain pack; modified Wright's stain; Bayer, Elkhart, IN) and one with a quick Romanowsky stain (Jorgensen Laboratories, Loveland, CO) for microscopic evaluation. The RBC count was calculated as the total cell count × % RBCs counted in at least 20 oil (×1000) fields. The TNCC was calculated as the total cell count minus RBC count. The Koret School of Veterinary Medicine – Veterinary Teaching Hospital (KSVM-VTH) Laboratory reference interval for CSF TNCC is ≤5 cells/μl. Differential counts (%) of neutrophils, lymphocytes, monocytes and macrophages were determined manually by counting 100 nucleated cells in the two stained slides. When the TNCC was <100, the differential count was based on all nucleated cells observed.

Monocytes were defined based on size (20–50 μm), a blue, slightly granular cytoplasm, a higher nuclear to cytoplasmic (N:C) ratio compared to macrophages, and none to a small number of discrete cytoplasmic vacuoles. Macrophages were defined based on size (>50 μm), lower N:C ratio compared to monocytes, lacy nuclear chromatin and highly vacuolated or foamy cytoplasm, sometimes containing phagocytized debris or presenting erythrophagia (Christopher et al., 1988). Lymphocytes were defined based on size (usually 10–15 μm) and a high N:C ratio, clumped heterochromatin, and an agranular cytoplasm.

Cytologic evaluation was done by a single experienced clinician (IA), who was blinded to the outcome of the dogs. In order to assess the reliability of the differential CSF counts, half of the samples were evaluated blindly by another clinician (SK). The inter-observer agreement was determined and the results were separately analyzed in association with the outcome.

CSF total protein (TP) concentration was measured using turbidimetry (Cobas –Mira, or Cobas-Integra 400 Plus, Roche, Mannheim, Germany; at 37 °C; Reagent, Roche Diagnostics, Mannheim, Germany). The KSVM-VTH Laboratory reference interval for CSF TP concentration is ≤25 mg/dl.

2.3. Statistical analysis

For analysis of the association of signalment and history parameters with CSF findings, dogs were divided into two breed groups, namely chondrodystrophic or non-chondrodystrophic. Dogs were also divided into two groups based on the presence or absence of prior steroid treatment. The TNCC and TP concentration and the percentages of each nucleated cell type were considered as continuous variables. For analyses of the outcome, dogs were divided into two outcome groups, namely dogs that regained DPP versus dogs that failed to regain DPP and dogs with successful versus unsuccessful outcome. Dogs were also divided into four groups based on the time

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