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Transcranial magnetic motor evoked potentials in Great Danes with and without clinical signs of cervical spondylomyelopathy: Association with neurological findings and magnetic resonance imaging

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ABSTRACT

Transcranial magnetic motor evoked potentials (TMMEPs) assess the functional integrity of the descending motor pathways, which are typically compromised in canine cervical spondylomyelopathy (CSM). The objective of this prospective study was to establish the reference ranges of TMMEP latency and amplitude in clinically normal (control) Great Danes (GDs), compare TMMEPs obtained in GDs with and without CSM, and determine whether there is any association between TMMEP data and severity of neurological signs or magnetic resonance imaging (MRI) findings. Twenty-nine client-owned GDs were enrolled (15 controls, 14 CSM-affected). All dogs underwent TMMEPs under sedation, and latencies and amplitudes were recorded from the extensor carpi radialis (ECR) and cranial tibial (CT) muscles. MRI of the cervical vertebral column was performed to evaluate the presence and severity of spinal cord (SC) compression, and the presence of SC signal changes.

ECR and CT latencies were significantly longer in CSM-affected than control GDs. No significant differences between groups were found for amplitudes or neuronal path lengths. For the CT TMMEPs, CSM-affected GDs with moderate and severe clinical signs had significantly longer latencies than those with mild clinical signs. Significantly longer CT latencies were found in dogs with moderate and severe SC compression compared with dogs with mild compression. CT TMMEPs could not be recorded in 7/9 CSM-affected GDs with SC signal changes. These results provide a reference range for TMMEPs of clinically normal GDs. The use of TMMEPs is a valid ancillary test to assess the integrity of motor pathways in GDs with CSM.

Introduction

The use of transcranial magnetic motor evoked potentials (TMMEPs) was first described in humans in 1985 (Barker et al., 1985). To obtain TMMEPs, a magnetic stimulator and a coil are used to apply a brief magnetic field to the motor cortex, which generates a recordable motor evoked potential in the contralateral appendicular muscles (Nollet et al., 2003). This technique provides a non-invasive method for assessing descending motor pathway function (Barker et al., 1985; Di Lazzaro et al., 1999).

In humans, TMMEPs have been used to evaluate the functionality of the motor pathways in cervical spondylotic myelopathy, which is a common cause of chronic compressive cervical myelopathy similar to canine cervical spondylomyelopathy (CSM) (Di Lazzaro et al., 1999; Lo, 2007; da Costa, 2010). Magnetic resonance imaging (MRI) is typically used to diagnose this human disease and define the compressive sites, but it cannot provide information about spinal cord (SC) functionality (Capone et al., 2013). In this human condition, TMMEPs can be used to detect preclinical myelopathy, monitor disease progression by obtaining serial recordings, and monitor SC function during surgery (Travlos et al., 1992; Lo et al., 2004, 2006; Capone et al., 2013).

The use of TMMEPs has been reported in horses and dogs with cervical SC disease (Nollet et al., 2002; Poma et al., 2002; da Costa et al., 2006; De Decker et al., 2011). In CSM-affected Doberman Pinschers, TMMEP latencies were increased when compared with clinically normal Dobermans, and correlated with the severity of neurological signs and MRI findings in affected dogs (da Costa et al., 2006; De Decker et al., 2011). Great Danes (GDs) are also frequently affected by CSM (da Costa, 2010). However, no study has reported TMMEPs values in clinically normal GDs or investigated its use in GDs with CSM. In humans and horses, TMMEP latencies are influenced by body size (Chu, 1989; Nollet et al., 2004). GDs are

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larger than Doberman Pinschers; thus, TMMEPs reference ranges obtained in Doberman Pinschers may not apply to GDs.

The purpose of this study was to establish the reference ranges of TMMEP latency and amplitude in clinically normal GDs, compare TMMEPs obtained in GDs with and without clinical signs of CSM, and determine whether there is any association between TMMEP data, severity of neurological signs, and MRI findings. We hypothesized that differences would be identified in the TMMEP latencies between clinically normal and CSM-affected GDs, but no amplitude differences would be identified between groups, similar to what has been previously reported in a TMMEP study performed in Dobermans with and without CSM (da Costa et al., 2006). We also hypothesized that TMMEP latencies would be longer in the CSM-affected GDs with more severe clinical signs and SC compression.

Materials and methods

Animals

The study was conducted in accordance with the guidelines and with the approval of The Ohio State University Clinical Research Advisory Committee and the Institutional Animal Care and Use Committee (2011A00000027). Written owner consent was obtained prior to study enrollment. Two groups of client-owned GDs were prospectively enrolled between April 2011 and October 2012. The first group included 15 clinically normal (control) GDs based on a normal neurological examination and no history of neurological disease. Only GDs ≥ 1 year of age were eligible for enrollment as control dogs. The second group included 14 GDs with clinical signs and neurological examination consistent with CSM and diagnostic confirmation via MRI. The time of onset of signs was recorded. A video of the gait of all CSM-affected dogs was obtained at the time of enrollment. All GDs were examined by the two investigators, and underwent TMMEPs and MRI of the cervical vertebral column.

Gait grading

The video material was reviewed at a later time by one investigator (PMV) to assign a neurological grade to each CSM-affected GD. At least 2 min of video material were available for all dogs. The gait was graded from 0 to 3 for each thoracic and pelvic limb as follows: grade 0, normal limb; grade 1, abnormal use of the limb <40% of the steps; grade 2, abnormal use of the limb between 40% and 70% of the steps, and grade 3, abnormal use of the limb >70% of the steps. Signs of both paresis/weakness (i.e., knuckling, scuffing, dragging) and/or ataxia/incoordination (inconsistent limb/foot placement) were considered as an abnormal use of the limb. If the grade assigned to the right and left thoracic limbs differed, the worse grade (from 0 to 3) was used as the overall grading for that pair of limbs. The same process was followed for the pelvic limb gait grading.

The thoracic limb grade (from 0 to 3) and the pelvic limb grade (from 0 to 3) were summed for each dog, producing an overall final gait grade ranging from 1 to 6 (no CSM-affected dog had four limbs characterized as normal, thus no overall final grade of 0 was possible). For the purpose of statistical analysis to investigate associations between disease severity based on gait grading and the TMMEPs, the overall final gait grades 1 and 2 were grouped and categorized as mild, grades 3 and 4 were categorized as moderate, and grades 5 and 6 were categorized as severe.

TMMEPs

Dogs were sedated with hydromorphone (0.05–0.1 mg/kg intravenously [IV]) and dexmedetomidine (4–8 μg/kg IV). The dogs were positioned in lateral recumbency. The technique of TMMEPs acquisition was based on previous studies (da Costa et al., 2006; De Decker et al., 2011). Transcranial magnetic stimulation was performed using a magnetic stimulator (Cadwell Sierra Wave, Cadwell Laboratories) and a 9.0 cm circular coil (Magstim, The Magstim Company) capable of producing a peak magnetic field of 2.0 Tesla at the coil surface. Supramaximal stimulus intensity (100% stimulus) was delivered by the magnetic coil held tangentially to the skull, with the center of the coil over the skull lateral to the vertex. The coil was kept in close contact with the skin, and the current flow within the coil ran in a clockwise direction. Four individual stimulations were delivered over the motor cortex before repeating the procedure on the opposite side.

Recordings of TMMEPs were obtained by use of an electromyography (Cadwell Sierra Wave, Cadwell Laboratories). Disposable13-mm non-insulated, stainless steel needles were used as the recording (active), reference, and ground electrodes (Technomed Europe, Medical Accessories). The recording electrode was inserted in the muscle belly of both the extensor carpi radialis (ECR) and cranial tibial (CT) muscles. The reference electrode was positioned subcutaneously 1 cm distal to the active electrode. The ground electrode was placed subcutaneously in the dorsal aspect of the cranial thoracic region. The recording electrode was connected to the negative input of the preamplifier, thus negativity of the recording electrode with respect to the reference electrode caused an upward deflection of the trace.

The TMMEPs were recorded from the right and left limbs after stimulating the respective contralateral cortex. The recorded TMMEP waveforms were displayed on the oscilloscope screen and saved. The total recording time was 100 ms. The low and high frequency filters were set at 30 Hz and 10 kHz, respectively. The sensitivity was set at 1000 μV/division for all recordings.

The latencies and amplitudes were measured using the manually directed cursors on the oscilloscope. Onset latencies were measured in ms and calculated as the interval from the onset of the stimulus to the onset of the response. Peak-to-peak amplitudes were measured in microvolts and calculated from the peak of the negative wave to the nadir of the first positive wave. When measuring latencies and amplitudes, the gain was adjusted as needed to optimize the visualization of waves and the manual placing of cursors to obtain latency and amplitude data. The neuronal path length of each dog was measured using a tape from the site of the transcranial magnetic stimulation to the active electrode located within the ECR and CT muscles contralateral to the stimulated site.

MRI

All dogs underwent MRI of the cervical vertebral column under general anesthesia with a 3.0 Tesla magnet (Achieva, Philips Healthcare) and a surface coil. Dogs were positioned in dorsal recumbency. Turbo spin-echo sagittal and transverse T2-weighted images (WI) were obtained and used to determine the sites of SC compression. Seven intervertebral spaces (C2-3 to T1-2) were imaged and five transverse slices obtained for every intervertebral space. All MRI studies were evaluated by one investigator (PMV) using dedicated software (E-Film Merge Healthcare). Spinal cord compression was graded as previously described (da Costa et al., 2012): mild (<25% reduction in the SC diameter), moderate (25–50% reduction), and severe (>50% reduction in the SC diameter). If more than one type of SC compression was present in the same dog, the most severe type of compression was used for statistical analysis. Sites of SC signal changes, defined as SC hyperintensity on T2-weighted images, were also recorded.

Statistical methods

For all TMMEP variables (latency, amplitude, and neuronal path length for the ECR and CT muscles), values recorded in each dog for left and right limbs were averaged to obtain a single value for each variable and dog. A random-effects linear regression model was used to compare the TMMEP variables between control and CSM-affected GDs, and to investigate associations between TMMEP latencies and amplitudes with the neurological status and MRI findings in CSM-affected GDs. Adjustments were made for age, gender, and weight. The P values were adjusted by Holm's procedure to conserve the type I error at 0.05. Significance was set at $P < 0.05$. Analyses were performed by use of computer software (Stata v.12.1, Stata Corporation).

Results

Clinical data and MRI findings

The clinically normal GDs included seven females (six spayed, one intact) and eight males (seven neutered, one intact). Their median age at the time of enrollment was 2.3 years (range, 1–6.4 years). The median weight was 52 kg (range, 40.5–73 kg). All clinically normal GDs had a normal neurological examination. The CSM-affected GDs included two spayed females, 11 neutered males, and one intact male. Their median age at the time of enrollment was 4.2 years (range, 1–7.2 years). The median weight was 57.5 kg (range, 45–79.3 kg). The reported median age at the onset of signs of CSM was 1.6 years (range, 0.4–4.2 years). The clinical signs had been present for a mean time of 1.6 years (range, 0.2–5 years) before enrollment. Thirteen out of the 14 CSM-affected dogs showed ambulatory tetraparesis with proprioceptive ataxia of all limbs, and one showed a hypertonic thoracic limb gait with ambulatory paraparesis and proprioceptive ataxia of the pelvic limbs. All CSM-affected GDs had delayed postural reactions involving all limbs, and five had mild neck pain.

Gait grading yielded the following results: grade 1, $n = 1$; grade 2, $n = 3$; grade 3, $n = 1$; grade 4, $n = 3$; grade 5, $n = 1$; grade 6, $n = 5$. For statistical analysis, four dogs were considered to have mild signs (grades 1–2), four had moderate signs (grades 3–4), and six had severe signs (grades 5–6). Overall, 43 sites of SC compression were