Case Report Rapport de cas

Clinical peripheral neuropathy associated with diabetes mellitus in 3 dogs

Megan J. Morgan, Charles H. Vite, Anant Radhakrishnan, Rebecka S. Hess

Abstract — Clinical and electrodiagnostic findings in 3 spontaneously diabetic dogs with clinical peripheral neuropathy (PN) are reported. Clinical signs of a PN may develop in diabetic dogs with adequate glycemic control. In addition, laryngeal paralysis may develop in association with diabetes mellitus in dogs with clinical PN.

Résumé — Neuropathie périphérique clinique associée au diabète sucré chez 3 chiens. Les données cliniques et électrodiagnostiques de 3 chiens atteints de diabète spontané avec neuropathie périphérique (NP) clinique sont rapportées. Les signes cliniques d'une NP peuvent se développer chez les chiens diabétiques dont la glycémie est contrôlée de façon adéquate. De plus, une paralysie laryngée peut se développer en association avec le diabète sucré chez les chiens montrant une NP.

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Case 1

An 8-year-old, intact male, rottweiler was examined at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) for a 6-month history of pelvic limb weakness that acutely deteriorated 2 wk prior to examination. The dog had a 3-year history of diabetes mellitus (DM) that was being treated with neutral protamine Hagedorn (NPH) insulin (Humulin-N; Eli Lilly, Indianapolis, Indiana, USA) 0.76 U/kg body weight (BW), SC, q12h. Serial blood glucose (BG) measurements performed 3 wk prior to examination indicated adequate glycemic control (BG concentration, 9.18 to 17.98 mmol/L).

Case description

Abnormal physical examination findings included severe pelvic limb paresis and mild proprioceptive ataxia. The pelvic limbs had postural deficits and moderate muscle atrophy. The dog's stretch reflexes and muscle tone were normal. The dog's ataxia was suggestive of thoracic (T)3-lumbar (L)3 spinal cord disease; however, the severe paresis and moderate muscle atrophy, coupled with only mild ataxia, suggested that L4-sacral (S)1 spinal cord, peripheral nerve, endplate, or muscle disease was also present.

Complete blood (cell) count (CBC) findings were normal, except for a mild thrombocytosis (4.2×10^9 platelets/L, reference range (RR), 1.77 to 3.98×10^9 platelets/L) Abnormal serum biochemical findings included hyperglycemia (glucose 20.4 mmol/L; RR, 3.6 to 6.28 mmol/L), hypocalcemia (calcium 2.33 mmol/L; RR, 2.45 to 2.92 mmol/L), hyperkalemia (potassium 5.4 mmol/L; RR, 3.9 to 4.9 mmol/L), hypoalbuminemia (albumin 21 g/L; RR, 25 to 37 g/L), increased alkaline phosphatase (ALKP) activity (190 U/L, RR 24 to 174 U/L), hypercholesterolemia (cholesterol 14.56 mmol/L; RR, 3.33 to 8.24 mmol/L), and a decreased anion gap (9 mmol/L; RR, 12 to 16 mmol/L). Urinalysis showed a urine specific gravity of 1.027 with 3 g/L of protein (+3). Aerobic culture of urine obtained by cystocentesis showed no bacterial growth. The urine protein to creatinine ratio was 1.26 (RR, < 1.0). Total T4, free T4, and TSH concentrations were normal.

Results from thoracic, lumbar, and sacral spinal plain radiographic films and a myelogram were normal. Cerebrospinal fluid (CSF) collected at the cisterna magna contained 0.37 g/L of protein (RR, < 0.25 g/L) and had a normal nucleated cell count of 1 nucleated cell/μL.

An electromyogram (EMG) performed prior to myelography showed spontaneous fibrillation potentials in the left epaxial muscles located at T1–T2. Sciatic/tibial motor nerve conduction velocity (MNCV) was decreased distally with nerve stimulation at the level of the tarsus and stifle and recording electrodes placed in a plantar interosseous muscle (22.6 m/s; RR, 68.2 +/− 1.4 m/s [1]). Sciatic/tibial MNCV with stimulation at the level of the greater trochanter of the femur and at the tarsus was also slow (40.4 m/s; RR, 62.2 +/− 2.1 m/s [1]). Sciatic/tibial MNCV with stimulation at the level of the greater trochanter of the femur and at the level of the stifle was faster

Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, 3900 Delancey Street, Philadelphia, Pennsylvania 19104-6010, USA.

Address all correspondence and reprint requests to Dr. Hess; e-mail: rhess@vet.upenn.edu

Dr. Morgan's current address is City of Angels Veterinary Specialty Center, 9599 Jefferson Blvd, Culver City, California, 90232, USA.

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(67.7 m/s; no published reference). The M-wave amplitude for the distal segment of the sciatic nerve was decreased (10 mV; RR, 23.6 +/− 2.1 mV [1]); the area under the curve was not calculated. The F-wave latency in the sciatic nerve was increased at 33.2 m/s (calculated expected velocity was 21.2 m/s), and the F ratio was increased at 2.5 (RR, 1.954 +/− 0.086) (2,3). Sensory nerve conduction velocities of the left tibial, left peroneal, and left radial nerves were also decreased at 34.1 m/s, 38.2 m/s, and 30.4 m/s, respectively (RR, 57 +/− 7 m/s, 52 +/− 5 m/s, 57 +/− 5 m/s, respectively [4]).

Biopsy of the common peroneal nerve showed axonal degeneration affecting approximately 14% of fibers and demyelination and remyelination in approximately 10% of fibers. Biopsy of the lateral cutaneous antebrachial nerve showed mild demyelination and remyelination affecting 2% of fibers.

Results from follow-up physical examinations 1 and 2 mo later showed improvement in the pelvic limb gait abnormalities; subsequently, the owner reported that the dog was walking normally just prior to an examination for severe respiratory distress, 3 mo after the initial examination. The owners elected euthanasia at that time, due to the severity of the dog's respiratory distress. Permission for a necropsy was not granted; therefore, the cause of the respiratory distress was not discovered.

Case 2

An 8-year-old, neutered female, Labrador retriever was referred with a 1-month history of DM and progressive pelvic limb weakness. Past medical history included a diagnosis of hypothyroidism and subsequent treatment with levothyroxine (Soloxine; Virbac Corporation, Fort Worth, Texas, USA) supplementation, 0.02 mg/kg BW, PO, q12h, for 6 y. The dog's total T4 concentration prior to referral was 97.5 nmol/L (RR, 13 to 52 nmol/L). Despite the increased total T4 concentration, the levothyroxine dose was not changed. Treatment with NPH insulin (Humulin-N; Eli Lilly), 0.26 U/kg BW, SC, q12h, had been started and gradually increased to 0.42 U/kg BW, SC, q12h, based on serial BG measurements by the referring veterinarian.

Case description

At the time of examination, the dog's clinical signs included lethargy, polyuria, polydipsia, weight loss, and a normal appetite.

Abnormalities noted on physical examination included increased respiratory rate and immature cataracts, bilaterally. Neurological examination revealed severe pelvic limb paresis with decreased muscle tone and muscle atrophy. Postural reactions and sciatic nerve stretch reflexes were diminished in the pelvic limbs, and patellar reflexes were absent, bilaterally. There were no signs of pain on palpation of the spine or upon manipulation of the neck, although signs of pain were noted upon extension of both hip joints. Differential diagnoses for the neurological abnormalities included lumbosacral spinal cord disease or PN. Disease of the coxofemoral joints was also suspected.

Results from a CBC and serum biochemical panel were normal. Urinalysis showed a urine specific gravity of 1.026 with 27.5 mmol/L (+3) of glucose and trace ketones. Aerobic culture of urine obtained by cystocentesis showed no bacterial growth.

Radiographically, the spine appeared to be normal and results of serologic tests for *Toxoplasma gondii* and *Neospora caninum* were negative. Findings on an EMG included many spontaneous positive sharp waves and fibrillation potentials in the extensor carpi radialis, quadriceps, and gastrocnemius muscles. The MNCV of the distal sciatic nerve was decreased between the tarsus and the stifle (31.9 m/s; RR, 62.2 +/− 2.1 m/s [1]), but faster between the stifle and the greater trochanter of the femur (60 m/s; no reference available). The M-wave amplitude was decreased (13 mV; RR, 23.6 +/− 2.1 m/s). The F-wave latency was increased at 27.6 m/s (calculated expected velocity was 21.4 m/s) and the F-ratio was also increased at 2.3 (RR, 1.954 +/− 0.086 [2,3]).

The dog was discharged and the NPH insulin dose was increased to 0.5 U/kg BW, SC, q12h. On day 41, the dog had normal results on neurological examination, and the BG concentration ranged from 6.49 to 13.48 mmol/L over a 12-hour period.

Case 3

A 10-year-old, neutered male, Labrador retriever was examined for a 1-month history of progressive pelvic limb weakness, polyphagia, weight loss, and lethargy. Past medical history included left arytenoid lateralization for laryngeal paralysis and pneumonia 1 mo previously. The dog had a documented history of untreated hyperglycemia (BG 17.82 mmol/L; RR, 3.58 to 6.16 mmol/L) and glucosuria (16.5 mmol/L, 3+) 1 mo prior to examination.

Case description

On physical examination, the dog had inspiratory stridor, increased respiratory rate, severe bilateral pelvic limb weakness, and atrophy of the pelvic limb muscles and the temporalis muscle. Orthopedic examination revealed a left cranial cruciate ligament rupture. Neurological examination revealed mild proprioceptive ataxia and severe pelvic limb paresis. Mildly diminished proprioception and moderately diminished sciatic and femoral nerve stretch reflexes were noted in both pelvic limbs. Poor flexion of both hock joints was noted when the toes were pinched. There was decreased pelvic limb muscle tone. Signs of mild pain were noted on palpation at the level of L7–S1. Lumbar spinal disease or PN was suspected.

Results from a CBC, 1 mo prior to evaluation, were normal. Results from a serum biochemical panel revealed hyperglycemia (BG 23.87 mmol/L; RR, 3.58 to 6.16 mmol/L), increased blood urea nitrogen (BUN) concentration (11.07 mmol/L; RR, 14 to 10.71 mmol/L), hypocalcemia (calcium 2.35 mmol/L; RR, 2.45 to 2.93 mmol/L), and increased activities of alanine aminotransferase (ALT) (143 U/L; RR, 16 to 91 U/L), aspartate aminotransferase (AST) (81 U/L; RR, 23 to 65 U/L), and alkaline phosphatase (SAP) (1188 U/L; RR, 20 to 155 U/L). Urine obtained via free catch was submitted for urinalysis, which showed a urine specific gravity of 1.036, with 3 g/L (+3) glucose, bilirubin (1+), moderate ketonuria, 1 g/L (2+) protein,

and an unremarkable sediment. Total T4, free T4, and TSH concentrations were not consistent with hypothyroidism.

A computed tomography (CT) scan of the spine revealed moderate protrusion of the L7–S1 intervertebral disk on extension of the pelvic limbs, and decreased protrusion with flexion of these limbs.

Electrodiagnostic testing showed slow distal ulnar nerve MNCV at 27 m/s (RR, 59.0 +/− 1.9 m/s [1]). The sciatic/tibial nerve MNCVs with stimulation at the tarsus and stifle, and with stimulation at the stifle and greater trochanter of the femur were slow (26 m/s and 35 m/s, respectively). The common peroneal nerve MNCV with stimulation at the stifle and greater trochanter of the femur and recording from the cranial tibial muscle was 43 m/s (RR, 79.8 +/− 1.8 m/s [1]). The amplitudes of all M-waves were less than 5 mV. The F-wave latency was 53.9 m/s. An expected latency could not be calculated, since the limb length was not recorded. The F-ratio was increased at 3.4 (RR, 1.954 +/− 0.086 m/s [2,3]). Positive sharp waves and fibrillation potentials were seen in both thoracic and pelvic limbs.

The dog developed progressive respiratory distress and hypoxemia after general anesthesia, and the owners elected that the dog be euthanized. Permission for necropsy was not granted; therefore, the cause of the respiratory distress was not determined.

Discussion

The frequency with which peripheral neuropathy (PN) occurs in dogs with diabetes mellitus (DM) is not known. Previous studies of canine diabetic neuropathy can be divided into those in which dogs with subclinical PN were examined (5–9), and those in which dogs with clinical signs of PN were examined (10–13). In 5 previous studies of 32 dogs with spontaneous or experimental DM and no reported neurological clinical signs, PN was confirmed by histopathologic or electrodiagnostic findings in most dogs (5–9). In contrast, clinical signs of PN associated with spontaneous DM have been reported in only 4 dogs from 4 different studies (10–13).

The diagnosis of a PN is supported by clinical signs, electromyographic abnormalities, nerve biopsies, and muscle biopsies (14,15). Clinical signs suggestive of a PN include weakness, muscle atrophy, hyporeflexia, and hypotonia (14–16). Electrodiagnostic abnormalities consistent with a diagnosis of PN include spontaneous electrical activity, decreased M-wave amplitude (suggestive of axonal disease), and markedly slow motor and sensory nerve conduction velocities (suggestive of demyelinating disease) (5,16–18). Histopathological findings consistent with PN are axonal degeneration with segmental demyelination and remyelination (8,9,14,16).

Diabetic humans are afflicted by a number of neuropathies including sensory neuropathies, focal and multifocal neuropathies, and autonomic neuropathies (18). The most common of these neuropathies, and the one that most resembles the neuropathy observed in diabetic dogs, is the chronic sensorimotor distal symmetric polyneuropathy (DPN) (18). Approximately 50% of human diabetics develop symptomatic DPN. However, approximately 50% of human diabetics with DPN are asymptomatic for the disease. Therefore, the American Diabetes Association recommends annual screening and examination of human diabetics in order to detect subclinical DPN (18). The veterinary literature suggests that, as in human diabetics, subclinical PN is more common than clinical PN in dogs with DM. It is also conceivable that prospective routine neurological screening of diabetic dogs may reveal that mild clinical neuropathy is more common than previously suspected (14). The 3 dogs reported here were all spontaneously diabetic dogs with confirmed PN that were seen at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) between 1988 and 2005. During the same time period, 319 diabetic dogs were examined at MJR-VHUP.

Clinical signs suggestive of PN in these patients included weakness (observed in all 3 dogs), muscle atrophy (observed in all 3 dogs), hyporeflexia (observed in 2 dogs), and hypotonia (observed in 2 dogs) (14–16). Two dogs (cases 1 and 3) had mild proprioceptive ataxia evident at the time of neurological examination with no evidence of significant T3–L3 spinal cord disease on imaging. Proprioceptive ataxia suggests the presence of undiagnosed T3–L3 spinal cord disease, but it could also be indicative of a neuropathy affecting the proprioceptive fibers of the peripheral nerve, resulting in ataxia similar to that seen in human diabetics (19).

Electromyography demonstrated spontaneous electrical activity and diminished nerve conduction velocity in all 3 dogs. The electrodiagnostic abnormalities seen in the pelvic limbs are consistent with either L4–S1 spinal cord or root disease or a PN (5,14,18). Dogs 1 and 2 had no evidence of significant lumbosacral disease on imaging, and signs of pain were not elicited in either dog upon spinal palpation. Dog 3 had evidence of mild L7–S1 intervertebral disk protrusion on a CT scan, which was judged to be insufficient to cause the clinical signs, given the expectation that the dog's hind limb proprioception would be diminished to a greater extent should the disk protrusion be the cause of the severe pelvic limb paresis and diminished stretch reflexes. Protrusion of a disk at this space could contribute to the electrodiagnostic abnormalities seen in the sciatic distribution, but it should not cause diminished femoral reflexes. In addition, there was slowing of the ulnar nerve MNCV, which, in combination with the slowed MNCV of the sciatic distribution, suggests a PN rather than lumbosacral disease as the cause of the dog's neurological abnormalities.

Spontaneous electrical activity and decreased M-wave amplitude are suggestive of axonal disease, and the degree of slowing of MNCV and sensory nerve conduction velocity are suggestive of demyelinating disease. These abnormalities were confirmed in dog 1 in which axonal degeneration and demyelination were found on histologic examination.

Electrodiagnostic testing did not readily distinguish whether proximal or distal nerve segments were more affected. In dogs 1 and 2, the MNCV of the proximal sciatic/tibial nerve was not as significantly affected as the MNCV of the distal sciatic/tibial nerve. However, the F-ratio was greater than expected, suggesting more involvement of the proximal segment of the nerve (17). It was been noted that limb length can significantly affect F-ratio measurements in dogs (20). Long-limbed dogs may have

longer proximal nerve segments, thus increasing the calculated F-ratio. In our study, all the increases in F-ratio were found in long-limbed dogs.

One of the dogs reported here had a recent previous medical history of laryngeal paralysis. Several cases of DM-associated laryngeal paralysis have been reported in the human medical literature (21–25). To our knowledge, this is the 1st report of laryngeal paralysis in association with DM in a dog with clinical PN.

One of the dogs in this study (case 1) had had DM for 3 y prior to the onset of acute clinical signs of a PN. This dog had adequate glycemic control just prior to the time the PN was diagnosed. Previously, clinical PN and spontaneous DM in dogs had been diagnosed within the same time frame (10–13). The present findings indicate that clinical signs of a PN may develop or progress long after the diagnosis of DM, despite apparently adequate glycemic control.

In humans with DM, hyperglycemia is a risk factor for neuropathies, and tight glycemic control is recommended for prevention and treatment of neuropathies (18). However, other factors, such as hyperlipidemia, hypertension, and duration of DM, also increase the risk of neuropathies in humans (18). Larger prospective studies of dogs with DM and peripheral neuropathies are needed to determine the importance of these factors in the development and progression of peripheral neuropathies in dogs.

The most significant strength of this report is that the cases discussed were all clinical patients. Based upon a combination of clinical evaluation, clinical laboratory testing, electrodiagnostic testing, imaging, and response to treatment, in all 3 cases, diabetic neuropathy is the best differential diagnosis for PN. However, because of the limitations inherent in investigating clinical cases, such as financial constraints and the need for owner consent to perform diagnostic testing, not all of the cases had diagnostic biopsies taken of peripheral nerves or muscles.

Author contributions

Dr. Morgan was involved with the cases, searched the medical records database, and wrote the manuscript. Dr. Vite assisted in the interpretation of the findings of the neurological examination, electrodiagnostic testing, and diagnostic imaging. Dr. Radhakrishnan cared for one of the dogs and assisted in preparing the case discussions. Dr. Hess assisted in the interpretation of the endocrinological aspects of the cases, supervised the care of one of the dogs, and assisted in the preparation of the manuscript. All authors read and approved the final manuscript. CVJ

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