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Review

Canine inherited motor and sensory neuropathies: An updated classification in 22 breeds and comparison to Charcot–Marie–Tooth disease

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ABSTRACT

Canine inherited neuropathies form a group of degenerative diseases affecting motor and/or sensory and autonomic peripheral nerves. There is now a large number of inherited motor and sensory neuropathies (IMSN) reported in the veterinary literature, for which clinical, electrophysiological, histopathological and mode of inheritance data are available. Their resemblance with Charcot–Marie–Tooth disease in humans is suggested, although direct comparison is difficult due to the small number of cases described in each breed and the lack of genetic knowledge in dogs. Charcot–Marie–Tooth disease forms a wide group of hereditary neuropathies for which a genetic mutation is recognised in more than 70% of patients. In dogs, no genetic mutation has so far been identified and the knowledge available for human hereditary neuropathies may be useful to identify genetic mutations in dogs. This review provides an update on data available on inherited neuropathy in Leonberger dogs and three new degenerative neuropathies are briefly described in two Russian Black terriers, two Cocker Spaniels and a Podhale Shepherd dog.

Introduction

A number of peripheral nervous system (PNS) diseases of degenerative, nutritional, metabolic, toxic, immunological, neoplastic or infectious origin are recognised in dogs (Duncan, 1980; Cuddon, 2002; Coates and O'Brien, 2004). This review focuses on degenerative neuropathies, some of which are 'inherited' because a familial link between the affected cases has been demonstrated, while for other cases, the term 'sporadic' is used because the degenerative process has no demonstrated familial link between the affected cases. Inherited and sporadic forms can manifest either at a young or old age.

Inherited and sporadic neuropathies can be 'syndromic' or 'non-syndromic'. Syndromic neuropathies are part of generalised degenerative processes of the central nervous system (CNS) and PNS (Coates and O'Brien, 2004). Dogs present with a collection of neurological signs (or 'syndrome') that cannot be explained by a single lesion of the CNS or a peripheral neuropathy alone. For example, globoid cell leukodystrophy, a storage disease affecting West Highland and Cairn terriers, causes cerebellar signs and a demyelinating neuropathy (Fletcher et al., 1966). Non-syndromic inherited neuropathies typically cause only clinical signs relating to a peripheral neuropathy and will be the main focus of this article.

The following terms are used: (1) *inherited motor and sensory neuropathy* (IMSN) when the neuropathy is mixed (motor and sensory); (2) *inherited sensory and autonomic neuropathy* (ISAN) when the neuropathy is only sensory and associated or not with autonomic dysfunction; and (3) *sporadic motor and sensory neuropathy* (SMSN) when the neuropathy is sporadic.

IMSN have been regularly identified in dogs over the last 50 years. Ten canine inherited neuropathies were described between 1964 and 1989, eight between 1990 and 1999, and five between 2000 and 2009, affecting a total of 19 breeds (Table 2). In this article, three new clinical entities are described that have been observed in two related Russian Black terriers, a Podhale Shepherd (sporadic case) and two Cocker Spaniels (sporadic cases). The primary aim is to provide the reader with an updated classification of canine inherited and sporadic neuropathies, but the clinical signs, electrophysiology, histopathology and mode of inheritance of canine inherited neuropathies as described in the veterinary literature are also reviewed.

Canine inherited neuropathies have often been described according to the clinical signs that they produce, such as '*laryngeal paralysis polyneuropathy complex*' in Dalmatians, Rottweilers or Pyrenean Mountain dogs (Braund et al., 1994a; Mahony et al., 1998; Gabriel et al., 2006). However, inherited neuropathies can also be separated in groups based on their histopathological phenotype, mode of inheritance, and motor or sensory clinical characteristics, as presented here. Indeed, the degenerative process of the peripheral nerves predominantly affects either the myelin sheath (directly or secondary to Schwann cell dysfunction) or the axon, so providing a useful criterion to distinguish the different types of neuropathies.

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The secondary aim of this review is to suggest a link but also highlight differences between canine inherited neuropathies and human hereditary motor and sensory neuropathies (HMSN). HMSN were first described by Drs. Charcot and Marie in Paris, and Dr. Tooth in Cambridge (Charcot, 1886). HMSN now form a wide group of degenerative neuropathies and are the most common hereditary neuromuscular disorder in humans, affecting 40 out of 100,000 individuals (Pareyson and Marchesi, 2009). Familial and sporadic forms occur (Pareyson and Marchesi, 2009). In the literature, authors refer to HMSN by using the term Charcot–Marie–Tooth (CMT) disease.

Here, CMT subtypes are named with their number following the abbreviation 'CMT'. For example, CMT type 1 is CMT1. Table 1 briefly describes the human forms of CMT disease and their phenotype. Although a link between canine IMSN and CMT disease is proposed, there is at present no genetic mutation identified in dogs to further support the comparison.

Clinical presentation of IMSN, SMSN and ISAN in dogs

IMSN typically produce lower motor neuron signs, i.e. decrease or loss of spinal reflexes. The clinical signs depend on the degree of involvement of motor and/or sensory fibres but are not specific to the underlying pathological process (i.e. demyelination or axonal loss). In both situations the disease leads to axonal degeneration, most often of the largest and longest fibres. The clinical signs usually start in the distal part of the legs and arms in humans (in a glove-and-stocking pattern) and distal part of the pelvic limbs in dogs (Coates and O'Brien, 2004; Pareyson and Marchesi, 2009).

Motor signs

The classical motor signs are weakness, hypotonia (often causing a palmigrade and plantigrade stance) and muscle atrophy secondary to denervation. Orthopaedic lesions can worsen the locomotor deficits and are sometimes considered as primary injuries, whereas they are in fact secondary to the neuropathy (e.g. due to lack of muscle support to the joints). Thus, it is important to conduct a neurological examination for animals with atypical gait deficits, especially when the orthopaedic injury is unusual in its onset and presentation. Giant breeds, such as Leonbergers (Shelton et al., 2003), Great Danes (Braund et al., 1980), Italian Spinones (Schatzberg and Shelton, 2004), Pyrenean Mountain dogs (Gabriel et al., 2006) and Podhale Shepherds (one case; NG, personal observation), frequently present with a characteristic high-stepping pelvic limb gait also called pseudo-hypermetria of the hock (see supplementary video). This gait compensates for the cranial tibial muscle atrophy with consequent dropping of the hock. Humans with CMT disease were historically described with a dropped foot by Charcot (1886), as a result of distal leg muscle atrophy.

Sensory and autonomic signs

In most degenerative neuropathies, dogs do not exhibit overt signs of pain (unless they develop neuropathic pain) and subtle dysaesthesia is difficult to detect clinically. Thus, the neuropathy may go undetected for a number of months to years. The classical sensory signs are ataxia, proprioceptive deficits and decreased sensation. Rarely, sensory deficits are the predominant sign and mainly cause loss of tactile, thermal and pain sensation. This leads to skin ulceration and auto-mutilations in dogs (Gnirs and Prelaud, 2005) and humans (Axelrod and Gold-von Simson, 2007; Auer-Grumbach, 2008). Sensory neuropathies are often accompanied by autonomic signs such as urinary incontinence, as observed in Border Collies (Wheeler, 1987; Harkin et al., 2005; Vermeersch et al., 2005), Long-haired Dachshunds (Duncan and Griffiths, 1982) and Jack-Russell terriers (Franklin et al., 1992), or thermal dysregulation in Dobermans with the 'dancing Doberman syndrome' (Braund, 2003).

Focal signs

Neuromuscular diseases in general can cause focal clinical signs, such as laryngeal paralysis, a change in the pitch of the bark, coughing, excessive panting, swallowing difficulties or food regurgitation (indicative of megaoesophagus). These signs are encountered with degenerative neuropathies and can be the only clinical abnormalities early in the course of the disease. Humans with CMT disease can present with upper airway disorders or voice changes (Aboussouan et al., 2007) and it is now well recognised that laryngeal paralysis and megaoesophagus in dogs are strong indicators of the presence of an underlying 'silent' neuropathy that may later progress (Gaber et al., 1985; Braund et al., 1989b; Gaynor et al., 1997; Jeffery et al., 2006; Vanhaesebrouck et al., 2008; Stanley et al., 2010). This finding should prompt electrophysiological

Table 1
CMT subtypes and their main associated phenotype; the 'typical' clinical phenotype corresponds to the predominance of distal limb-muscle wasting, weakness, and sensory loss, with proximal progression over time. CMT subtypes can be further divided but the reader is referred to the literature for more details (Suter and Scherer, 2003; Axelrod and Gold-von Simson, 2007; Pareyson and Marchesi, 2009).

CMT subtype	Inheritance	Histopathological phenotype	Clinical and electrophysiological phenotype
CMT1	AD	Demyelination, onion bulbs, secondary axonal degeneration	Typical phenotype, onset first and second decades of life, motor and sensory NCVs < 38 m/s upper-limb
CMT2	AD or AR	Chronic axonal loss	Typical phenotype, onset first to third decades of life, motor NCVs > 38 m/s upper-limb
CMTX	X-linked	Axonal loss and some demyelination	Typical phenotype, men > women, any age, motor NCVs intermediate (30–45 m/s upper-limb)
Intermediate CMT	AD	Axonal loss and some demyelination	Typical mild to moderate phenotype, onset between 2 and 50 years, motor NCVs intermediate (25–45 m/s upper-limb)
CMT3 and CHN	AD or AR	Severe dysmyelination, onion bulbs	Severe weakness, distal muscle atrophy and sensory loss, congenital onset, very slow NCVs, CHN: hypotonia at birth, very slow NCVs
CMT4	AR	Demyelination	Severe typical phenotype, vocal cord paresis, sensorineural deafness, facial and diaphragmatic weakness, early childhood onset, NCVs < 38 m/s upper-limb
HSAN	AD or AR	Predominantly axonal damage	Distal sensory loss (pain, temperature), chronic skin ulceration, autonomic disturbances, onset between second to fifth decades of life, lack of sensory potentials

AD, autosomal dominant; AR, autosomal recessive; CHN, congenital hypomyelinating neuropathy; CMT, Charcot–Marie–Tooth disease; HSAN, hereditary sensory and autonomic neuropathy; NCVs, nerve conduction velocities.