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Review

Canine degenerative myelopathy: a model of human amyotrophic lateral sclerosis

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ABSTRACT

Canine degenerative myelopathy (CDM) represents a unique naturally occurring animal model for human amyotrophic lateral sclerosis (ALS) because of similar clinical signs, neuropathologic findings, and involvement of the superoxide dismutase 1 (SOD1) mutation. A definitive diagnosis can only be made postmortem through microscopic detection of axonal degeneration, demyelination and astroglial proliferation, which is more severe in the dorsal columns of the thoracic spinal cord and in the dorsal portion of the lateral funiculus. Interestingly, the muscle acetylcholine receptor complexes are intact in CDM prior to functional impairment, thus suggesting that muscle atrophy in CDM does not result from physical denervation. Moreover, since sensory involvement seems to play an important role in CDM progression, a more careful investigation of the sensory pathology in ALS is also warranted. The importance of SOD1 expression remains unclear, while oxidative stress and denatured ubiquinated proteins appear to play a crucial role in the pathogenesis of CDM. In this updated narrative review we performed a systematic search of the published studies on CDM that may shed light on the pathophysiological mechanisms of human ALS. A better understanding of the factors that determine the disease progression in CDM may be beneficial for the development of effective treatments for ALS.

Contents

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating motor neuron disease, caused mainly by the abnormal accumulation of inclusions in the spinal cord (Bruijn et al., 2004). Most ALS cases (~90%) are sporadic without known genetic factors, and only a few cases have been known to exhibit a family history (Robberecht and Philips, 2013). Dominant mutations in superoxide dismutase-1 (SOD1), which encodes cytosolic Cu/Zn superoxide dismutase, have been identified as one of the major genetic causes of familial ALS (Rosen et al., 1993; Al-Chalabi et al., 2012). In addition, mutant SOD1 proteins have been known to accumulate abnormally in the form of insoluble inclusions within affected spinal motor neurons (MNs) of SOD1-related ALS patients (Bruijn et al., 1998).

Canine degenerative myelopathy (CDM) has been recognized for >40 years as a spontaneously occurring, adult-onset neurodegenerative spinal cord disorder, characterized by progressive impairment of motor functions (Averill, 1973). Because of similar lesions and the involvement of SOD1 mutation, CDM represents the first known solely naturally occurring animal model for human ALS. CDM shares many similarities with some forms of human ALS. In particular, the progression of the disease and the distribution of lesions are similar to those reported for the upper motor neuron (UMN)-dominant onset form of ALS (Engel et al., 1965; Hirano et al., 1967).

In this review article, we will focus on the studies that have investigated the pathophysiological mechanisms as well as the clinical and neuropathological findings associated with SOD1-mutation in both clinical entities, the CDM and the ALS. A literature search was conducted using the electronic databases MEDLINE, accessed via Pubmed (1966 to April 2014), and EMBASE (1980 to April 2014), and the medical subject headings (MeSH) "canine degenerative myelopathy", "amyotrophic lateral sclerosis", and "superoxide dismutase 1 (SOD1) mutation".

2. Signalment

CDM was first recognized as a specific neurological disease in 1973 (Averill, 1973). CDM was initially thought to be specific to German Shepherds; it has therefore also been known as German Shepherd dog myelopathy (Braund and Vandevelde, 1978). Since these early reports, CDM has been diagnosed in several other breeds as well. From clinical signs, genetic testing, and spinal cord histopathology, CDM has been found to occur in many breeds and is especially prevalent in Boxers (Awano et al., 2009; Miller et al., 2009) and Pembroke Welsh Corgis (PWCs) (Awano et al., 2009; Coates and Winiger, 2010). Nevertheless, the disease is also common in other breeds including the Rhodesian Ridgeback (Coates and Winiger, 2010), Siberian Husky (Bichsel et al., 1983), Miniature Poodle (Matthews and de Lahunta, 1985), Chesapeake Bay Retriever (Coates et al., 2007), Irish Setter, Dalmation, Weimaraner, Great Pyrenees, Samoyed, and Briard.

Most dogs are at least 8 years old before the onset of clinical signs (Averill, 1973; Griffiths and Duncan, 1975; Braund and Vandevelde, 1978; Bichsel et al., 1983; Matthews and de Lahunta, 1985; Johnston et al., 2000; Coates et al., 2007; March et al., 2009). The disease's duration can exceed 3 years; however, dog owners usually elect euthanasia within a year of diagnosis when their dogs become paraplegic (Coates and Winiger, 2010).

3. Clinical features

Initial clinical signs are seen in dogs 8 years or older and include loss of coordination due to asymmetric proprioceptive ataxia, and asymmetric spastic paraparesis, which progress to paraplegia within 1 year from clinical onset. Since patellar hyporeflexia and nerve root involvement were initially reported, the disease was first termed chronic degenerative radiculomyelopathy (Griffiths and Duncan, 1975).

Dog owners often elect euthanasia when their dogs become paraplegic (Coates and Wininger, 2010). If dogs are not euthanized during early stages and the disease is allowed to progress, clinical signs will ascend to the thoracic limbs and progress to include flaccid tetraplegia, widespread muscle atrophy, and difficulty swallowing (Averill, 1973; Matthews and de Lahunta, 1985; Coates et al., 2007; Coates and Wininger, 2010).

For many years, CDM was thought to be a disease that primarily involved the ascending and descending tracts of the spinal cord and not the peripheral nervous system (Averill, 1973; Griffiths and Duncan, 1975). At onset, enhanced spinal reflexes are consistent with UMN loss. Spinal cord pathology is most evident in the thoracic spinal cord early in the disease, spreads cranially and caudally, and becomes more severe as the disease progresses (Averill, 1973; March et al., 2009). Clinical disease progression in CDM is similar to that reported for the UMN-onset ALS, with UMN signs in the affected dogs progressing to lower motor neuron (LMN) signs (Brooks et al., 2000; Coates et al., 2007; Coates and Wininger, 2010). Upper limb hyporeflexia of the myotatic and withdrawal reflexes occurs in the late stage of the disease (Averill, 1973; Griffiths and Duncan, 1975; Bichsel et al., 1983; Matthews and de Lahunta, 1985; Coates et al., 2007).

4. Genetic and molecular findings

A key link between CDM and ALS are genetic similarities. Mutations in SOD1 account for approximately 20% of the familial ALS cases (Dion et al., 2009).

Awano and colleagues first reported in 2009 that dogs with CDM were homozygous for the A allele of a SOD1 missense mutation, SOD1:c.118G → A, which predicts a p.E40K amino acid mutation in SOD1 (Awano et al., 2009). More recently, the same research group described a dog which was homozygous for the T allele of a different SOD1 missense mutation, SOD1:c.52 A → T, which predicts a p.T18S amino acid substitution (Zeng et al., 2014).

In order to assess the distribution of SOD1:c.118A and SOD1:c.52T in 222 breeds, DNA from 33,747 dogs was genotyped at SOD1:c.118, SOD1:c.52, or both, and spinal cord sections from 249 dogs were examined (Zeng et al., 2014). The SOD1:c.118A allele was found in cross-bred dogs and in 124 different canine breeds whereas the SOD1:c.52T allele was only found in Bernese Mountain Dogs. Most of the dogs with histopathologically confirmed CDM were SOD1:c.118A homozygotes, but 8 dogs with histopathologically confirmed CDM were SOD1:c.118A/G heterozygotes and had no other sequence variants in their SOD1 amino acid coding regions (Zeng et al., 2014).

Interestingly, not all dogs homozygous for the SOD1 mutation develop CDM, and none of the dogs that were heterozygous for this mutation developed the disease. This is consistent with a previous study which reported that the SOD1 mutation in CDM is associated with an incompletely penetrant autosomal recessive mode of

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