CANINE DEGENERATIVE MYELOPATHY – PATHOGENESIS,
CURRENT DIAGNOSTICS POSSIBILITIES AND BREEDING
IMPLICATIONS REGARDING GENETIC TESTING

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ABSTRACT
Canine Degenerative Myelopathy (CDM) is an incurable, chronic, slow progressive, autoimmune disease of the canine spinal cord affecting older dogs, medium to large breeds. Etiopathogenesis is still unknown but the latest data show that mutation of superoxide dismutase 1 gene (SOD1) is known to cause amyotrophic lateral sclerosis (ALS) in humans. That is why CDM is a canine model of ALS. The initial clinical sings of spinal cord dysfunction (ataxia, spastic paresis, paraplegia) are commonly mistaken with other common problems (hip dysplasia or intervertebral disc disease). The antemortem diagnosis requires exclusion of them all but definitive confirmation of CDM requires pathologic examination of spinal cord tissue. There is no treatment available but novel therapies are promising. The DNA test is a commercially available tool to help breeders avoid producing CDM “at risk” offspring what significantly reduces the frequency of mutated alleles in future generations.

Key words: canine degenerative myelopathy, chronic degenerative radiculomyelopathy, progressive disease of the canine spinal cord

INTRODUCTION
Canine Degenerative Myelopathy (CDM) also known as a chronic degenerative radiculomyelopathy (CDR) is an incurable, chronic, adult onset, slow progressive disease of the canine spinal cord. It was first described almost 50 years ago [Averill 1973] and autoimmune reactions are listed among its causes. Degeneration of the spinal white matter is thought to be the pathological mechanism, underlying the disease. Immune system attacks myelin sheath around neurons in spinal cord especially in lumbar and thoracic region, breaking it down, resulting in loss of communication between nerves in lower body of the animal and the brain then muscle atrophy and paralysis. At the beginning, upper motor neuron spastic paraparesis and general proprioceptive ataxia in the pelvic limbs progress to a flaccid lower motor neuron tetraparesis [Coates and Wininger 2010]. Symptoms typically occur in elderly dogs, e.g. about 8 years in German Shepherds [Holder et al. 2014]. Initially, instability and lack of co-ordination of hind limbs is observed, followed by inability of urination and defecation. Eventually, front limbs are also paralysed and the dog cannot move, which happens after 9–18 months after the first symptoms occur. Affected animals, rather males than females, do not show symptoms of pain [Holder et al. 2014]. Usually most dogs are subjected to euthanasia at around one year from the first symptoms and only few owners decide to support their pets with a wheel cart. Prognosis is always bad. In Welsh Corgi Pembroke, a breed prone to the disease, the average age of euthanized dogs is about 13 years [Coates et al. 2007] and this corresponds to the breed average life expectancy. Not only is CDM of interest of veterinarians, but also of human neurologists, as it can be an animal model of human Amyotrophic Lateral Sclerosis (ALS, Lou Gehring’s disease) for novel therapeutic methods establishment comparing pathogenic mechanisms while conveying perspectives to translational medicine [Gurney et al. 1996, Coates and Wininger 2010]. Apart from transgenic mice used as a small animal...
model in experiments [Heiman-Patterson et al. 2011], there is no other animal species with spontaneous diseases occurrence. Currently, dogs that suffer from CDM can be treated with novel therapies, clinical improvement can be strictly monitored what in the future can be introduced into human patients with ALS. CDM has been yet described in more than 120 breeds of dogs and the most commonly affected ones are listed below in alphabetical order: Bernese Mountain Dog, Boxer, Borzoi, Chesapeake Bay Retriever, German Shepherd, Golden Retriever, Kerry Blue Terrier, Pembroke Welsh Corgi, Pug, Pyrenean Mountain Dog, Rhodesian Ridgeback, Shetland Sheepdog, Soft Coated Wheaten Terrier, Standard Poodle, Wire Foxterrier [Orthopedic Foundation for Animals 2018]. However, it has to be noted that in the cohort of 432,467 dogs examined at USA university clinics in the years 1990–1999, the number of histopathologically diagnosed CDM cases is a mere 0.19%, with the highest frequency observed in German Shepherds (2.01%). CDM was also found in mixed breeds and mutts [Zeng et al. 2014]. Such a low frequency can be attributed to the fact that only a small number of dogs, euthanized due to mobility loss, are subjected to post-mortem and histopathological examination of the spinal cord. On the other hand, it can be presumed that dogs with CDM symptoms are more frequently admitted and treated at university clinics than in small, private practices.

Advanced diagnostic imaging equipment like mobile C-arm fluoroscopic X-ray system, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scanners as well as biomedical research facilities are essential to perform variety of diagnostics and minimally invasive surgical procedures related with therapy attempts. Therefore, the percentages quoted can be even higher than the average in the total canine population. Non-invasive (non-surgical) diagnostic method is required that would allow to estimate the actual disease rate in the canine population.

DIAGNOSTICS

Differential diagnosis of CDM with histopathological examination of the spinal cord is difficult if at all possible as the same or very similar symptoms are observed in other diseases. The first to be excluded is intervertebral disc disease (IVDD) which is the major cause of hind limbs paralysis in dogs also the others like benign tumours, traumas, cysts or cerebral stroke. Even when each of those is excluded, the large spectrum of neurological degenerative disorders of the spinal cord is to be taken into consideration.

Neither Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) nor electromyography (EM) and cerebrospinal fluid (CSF) examination are specific enough to establish the diagnosis of CDM [Clemmons 1992, Coates 2004]. Therefore, such diagnosis can be only indicative and serves mainly to exclude other, similar diseases; some of them, contrary to CDM, are treatable or long-term palliative care is necessary. CT, MRI, ER and CSF collection require general anaesthesia what provides safety and lack of pain to the patient. Still it is inseparably/integrally associated with risk of complications.

Considering advantages and disadvantages of performing an examination using diagnostic imaging techniques it is essential to remember about possibility of subsequent surgery or other therapeutic procedures and to give an appropriate care, including usage of suitable drugs and proper minimally invasive anesthetic protocols, to minimize the level of mortality and morbidity during additional tests [Siewruk et al. 2017].

HISTOPATHOLOGY

Definite diagnosis of CDM can be only established post-mortem, after histopathological examination of the white matter of the thoracic region of the spinal cord. The picture corresponds to a non-inflammatory degeneration of axons. At more advanced stages nerve fibres atrophy, caused by degeneration of axons and secondary demyelination, is observed both in sensory and motoric nerves [Braud and Vandervelde 1978]. Cytoplasmic inclusions that bind anti-superoxide dismutase (SOD1) antibodies are found in the soma, together with immunological complexes [Barclay and Haines 1994, Coates et al. 2007].

TREATMENT POSSIBILITIES

CDM and ALS are irreversible, progressive diseases that cannot currently be cured in animal and human patients. However, physiotherapy and special diet can slow progression of muscle weakness and loss and lack of coordination and increase survival time. Canine hydrotherapy is more useful than walking when it is still possible but at the end dog wheelchair allows them to remain active and maintain its quality of life. Therefore, there is urgent need to introduce novel therapeutic methods into animal and human medicine. Glial-restricted progenitor cells (GRPs) hold great promise as a cellular therapeutic for the treatment both denyelinating and neurodegenerative diseases of central nervous system (CNS) [Sandrock et al. 2010]. This is a neural cell population that gives rise to astrocytes and oligodendrocytes in vitro and in vivo and makes the cell useful for clinical application [Herrera et al. 2001] in treatment of CDM and ALS. Introducing first into veterinary medicine allows for establishment of the save administration method and clinical effects monitoring. Glial precursor cells express A2B5 are breakthrough hope in treatment process what needs further de-
talyzed research [Gregori et al. 2002]. Fernández-Trapro et al. [2017] investigated whether similar CB2 receptor upregulation, as well as parallel changes in other endocannabinoid elements, is evident in the spinal cord of dogs with degenerative myelopathy (DM), caused by mutations in the superoxide dismutase 1 gene (SOD1). The results of their research indicated that significant up-regulation of CB2 receptors in the spinal cord in canine DM, which is concentrated in activated astrocytes. Therefore, CB2 receptors can be used in the future as a potential target to enhance the neuroprotective effects exerted by these glial cells. More over DM in dogs reproduces main features of human ALS (Amyotrophic Lateral Sclerosis) including loss of motor neurons, dysregulation of energy supply to neurons, and loss of myelin, and as such is an ideal model system for highly translational studies on therapeutic approaches for ALS [Golubczyk et al. 2019].

GENETIC TESTING

SOD1 – the genetic risk factor for CDM was described in several studies, population for the first time in 2009. SOD1 mutation in homozygotic status was confirmed with histopathologic analysis as the main causative factor of CDM but apart that there are many dogs suffering from CDM without SOD1 mutation. However, there are many more genetic factors important for CDM development. The U.S. Orthopedic Foundation for Animals released to the market the DNA test especially dedicated for breeders and dog owners.

Super Oxide Dismutase (SOD) is an enzyme, consisting of protein and catalyst parts, involved in dismutation of superoxide radicals to hydrogen peroxide. Three isoforms of superoxide dismutase were found: cytoplasmic (SOD1), mitochondrial (SOD2) and secreted outside the cell (SOD3). SOD1 is a highly resistant protein; it is not denatured in high temperatures and in the presence of other denaturising factors and also maintains stability over a wide pH range. However, it is susceptible to the action of different proteolytic enzymes [Imlay and Imlay 1996]. Its catalytic activity has been demonstrated in disposing of singlet oxygen (activated oxygen form) which is formed during inflammatory processes. Singlet oxygen is a potent oxidant, reacting with lipids and leading to their peroxidation. Mutations within SOD1 gene are known to result in changes in protein conformation and function. Such altered conformation prevents transport along the axons of motor nerves, which eventually leads to their death. In domestic dogs the SOD1 gene is located in chromosome 31.

In their studies Awano et al. [2009] and Zeng et al. [2014] demonstrated the relationship between the presence of the SOD1: c. 118 G > A mutation (exon 2) within the encoding gene for SOD1, and the occurrence of degenerative myelopathy in 124 breeds and crossbreeds of dogs, and the presence of another mutation – SOD1: c. 52 A > T (exon 1) which is found exclusively in Bernese Mountain Dogs [Zeng et al. 2014]. Having studied the inheritance mode, they concluded that both mutations are recessive and the disease can manifests in homozygous recessive individuals, possessing two copies of the mutated allele. Same authors conducted histopathological examinations and found that double mutation was typical in individuals diagnosed with CDM (n = 75). However, the same picture was found with 8 SOD1: c. 118 G > A heterozygous specimens. The authors conclude that homozygous SOD1: c. 118 G > A individuals are more likely to develop DM that the heterozygous SOD1: c. 118 G > A ones.

STATISTICS

The most comprehensive studies have been done on the occurrence of the SOD1: c. 118 G > A and SOD1: c. 52 A > T mutation in 33746 dogs of 222 breeds and crossbreds in the USA. Of those 49% were homozygous for the ancestral allele, 27% heterozygous and 24% homozygous for the mutant allele. The frequency of the mutant SOD1 allele between different breeds was highly variable [Zeng et al. 2014]. In several breeds, namely Weimaraner (n = 112 individuals); Great Dane (n = 84); Field Spaniel (n = 75); Basenji (n = 59); Akita (n = 58); English Cocker Spaniel (n = 56); Great Swiss Mountain Dog (n = 53); Bouvier des Flandres (n = 51); Dachshund (n = 50) no mutation was found. Interestingly, it occurred at very low frequency (0.07, 533 individuals) in Standard Poodles, which are nonetheless known to relatively often suffer from DM. The highest frequency was found with Wire Foxterriers, 0.94 (79 individuals). Similar studies from Germany (2009–2016) [Bauer et al. 2017] on 22,273 dogs demonstrated significantly lower frequency of the SOD1: c. 118 G > A mutation in the European populations of Pembroke Welsh Corgis and Australian Shepherds. Table 1 shows results from the above quoted studies (for breeds with minimum 500 individuals tested). The mutation was also found in mutts (309 individuals tested), 41%, were carries (heterozygotes) and 13% at risk (recessive homozygotes). In case of mutts, however, without organisational support from breed clubs which encouraged testing, it can be presumed that mostly those that showed some symptoms were tested. Results show that the mutation is widespread and probably quite old, not specific, as it can be found in the primordial, ancient breeds.

One of the breeds with strikingly high occurrence of the SOD1: c. 118 G > A is Welsh Corgi Pembroke (A allele frequency 0.79); it is also present in Welsh Corgi Cardigan (A allele frequency 0.32) yet in this case is far less common. Also, as this breed is numer-
Fiszdon, K., Gruszczyńska, J., Siewruk, K. (2020). Canine Degenerative Myelopathy – pathogenesis, current diagnostics possibilities and breeding implications regarding genetic testing. Acta Sci. Pol. Zootechnica, 19(1), 3–10. DOI: 10.21005/asp.2020.19.1.01

### Table 1.
Frequencies of the mutant SOD1: c 118 G > A allele in German [Ivansson et al. 2016] and American [Bauer et al. 2017] studies.

| Breed – Rasa | German data – Dane niemieckie | American data – Dane amerykańskie |
|--------------|-------------------------------|-----------------------------------|
| Hovawart – Hovawart | 0.40 | 0.34 |
| Welsh Corgi Pembroke – Welsh Corgi Pembroke | 0.38 | 0.79 |
| German Shepherd – Owczarek niemiecki | 0.37 | 0.37 |
| Collie – Collie | 0.36 | 0.39 |
| Bernese Mountain Dog – Bernelski pies pasterski | 0.32 | 0.38 |
| Czechoslovakian Wolfdog – Wilczak czechosłowacki | 0.27 | 0.34 |
| Borzoi – Borzoj | 0.23 | 0.17 |
| White Swiss Shepherd – Biały owczarek szwajcarski | 0.15 | — |
| Australian Shepherd – Owczarek australijski | 0.14 | 0.41 |
| Rhodesian Ridgeback – Rhodesian Ridgeback | 0.07 | 0.28 |
| Boxer – Bokser | — | 0.72 |
| Chesapeake Bay Retriever – Chesapeake Bay Retriever | — | 0.37 |
| Kerry Blue Terrier – Kerry Blue Terrier | — | 0.34 |
| Cardigan Welsh Corgi – Cardigan Welsh Corgi | — | 0.32 |
| Borzoi – Borzoj | — | 0.17 |
| Poodle Standard – Pudel Standard | — | 0.07 |

... (rest of the text)
and welfare of pure bred dogs. In case of DM, however, the matter seems to be rather complicated. As shown by Zeng et al. (2014), although histopathological examination confirmed DM in 60% of homozygous SOD1 mutant individuals, the disease was also confirmed in 4% heterozygous and 6% out of 53 homozygous, “clear” dogs. Therefore, in this case using the “At Risk” label seems to be more appropriate than “Affected” as a positive result indicates the risk of disease, but not the inevitability of its occurrence. Apart from the presence of the mutation, other factors, including environmental influences, are to be considered in DM etiology.

Currently many breeders are taking advantage of genetic testing and some of them tend to treat its results as the sole selection criterion. They exclude from breeding homozygous SOD1: c. 118 G > A individuals together with heterozygous carriers. This seems to be an effective tool in reducing the frequency of the mutant allele and a fast track to improving health status in the population. However, as stated by Bell [2005], genetic testing is a double-edged sword and its reckless use can ruin the breed instead of improving it. Gene pools of each breed are practically closed and it is important to maintain them as diverse as possible, especially in case of numerically small breeds, otherwise a breed cannot develop and falls into decline.

CONCLUSIONS

Our knowledge of the functions of all DNA fragments is limited yet it can be presumed that with decreased diversity also some desirable alleles can be easily lost and the frequencies of other than tested, possibly even more serious and dangerous mutations/diseases may increase. Genetic testing is a useful tool, preventing from indiscriminate breeding of affected and carrier individuals, yet in case of a widespread mutation more cautious breeding strategies are to be employed to avoid narrowing of the gene pool [Holder et al. 2014]. In breeds with some 1/3 of the population being “carriers”, instant elimination of such a large percentage of animals would undoubtedly have strong and negative impact on their gene pools. In such cases breeding strategies should aim at producing healthy individuals yet in the same time maintaining genetic diversity of the population as the presence of mutant alleles is less dangerous. Ideally, carriers should be only mated to “clear” individuals and progeny tested. Thus, although the mutant allele is still present, no affected progeny will be born. Similarly, in very small populations, affected animals can be also used, provided they are of outstanding merits and are mated to clear specimens only. The resulted progeny will be all carriers, but healthy. In this way undesirable alleles will stay under control. Unfortunately, in case of breeds with the highest frequency of the SOD1: c. 118 G > A mutation, even these strategies may result in dangerously narrowed gene pool, as numbers of clear individuals are very low [Holder et al. 2014].

ACKNOWLEDGEMENTS

The authors would like to thank Mirosław Redlicki from the Polish Kennel Club for substantive discussions that inspired them to write of this article.

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MIELOPATIA ZWYRODNIENIOWA PSÓW – PATOGENEZA, OBECNE MOŻLIWOŚCI DIAGNOSTYCZNE I IMPLIKACJE HODOWLANE DOTYCZĄCE BADAŃ GENETYCZNYCH

STRESZCZENIE
Mielopatia zwyrodnieniowa psów (CDM) jest nieuleczalną, przewlekłą, powoli postępującą, autoimmunologiczną chorobą rdzenia kręgowego psa, dotykającą starsze psy ras średnich i dużych. Jej etiopatogeneza jest nadal nieznana, ale najnowsze dane wskazują, iż za jej wystąpienie odpowiedzialna jest mutacja genu dysmutazy 1 nadtlenku (SOD1). Mutacja tego genu powoduje stwardnienie zanikowe boczne (ALS) u człowieka, dlatego też CDM jest zwierzęcym modelem ALS. Początkowe objawy kliniczne dysfunkcji rdzenia kręgowego (ataksja, niedowład spastyczny, paraplegia) nierzadko są mylone z objawami innych, bardziej powszechnie występujących chorób. Diagnoza postawiona za życia zwierzęcia wymaga ich wykluczenia, ale ostateczne potwierdzenie wystąpienia/ wykluczenia CDM może nastąpić poprzez przeprowadzenie patologicznego badania tkanki rdzenia kręgowego. Obecnie nie ma dostępnego leczenia CDM, ale nowe terapie są obiecujące i dają nadzieję na przyszłość.

Test DNA jest komercyjnie dostępnym narzędziem, które pomaga hodowcom uniknąć kojarzenia nosicieli CDM, co znacznie zmniejsza częstotliwość występowania zmutowanych alleli w następnych pokoleniach.

Słowa kluczowe: mielopatia zwyrodnieniowa psów, przewlekła zwyrodnieniowa radiculomielopatia, postępująca choroba psiego rdzenia kręgowego
