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PATHOLOGY OF THE CANINE AGING BRAIN: AN ANIMAL MODEL OF HUMAN NEURODEGENERATIVE DISEASES

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Summary

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The neurodegenerative diseases, and more specifically Alzheimer's disease (AD) and Parkinson's disease (PD), are problems with great importance for the public health, affect a large number of population and especially individuals of an older age. Animal models contribute to increase the knowledge on the pathophysiology of neurodegenerative diseases. Aged dogs spontaneously develop many features of aging and Alzheimer's disease including cognitive decline and neuropathology. The canine appears to represent a useful spontaneous model for understanding the early changes and their interrelationships in Alzheimer's disease and senile dementia of Alzheimer's type in humans. The key to preventing behavioural problems is to help owners to understand a problem why their dogs behave in the way they do and to help them to manage, modify or accept the behaviours. The disease is currently diagnosed only via clinical assessments and confirmed by postmortem brain pathology. The development of validated biomarkers for Alzheimer's disease is essential to improve diagnosis and accelerate the development of new therapies. The pathologic processes of AD start decades before the first symptoms. So several cerebrospinal fluid and blood biomarkers may provide means of early disease detection.

Key words: aging, Alzheimer's disease, biomarkers, brain, canine, oxidative stress

The incidence of neurodegenerative diseases increases with age and, considering the aging process of the population worldwide, the prevalence of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) is expected to rise in the next years. This is particularly true for AD, the most common form of dementia, accounting for approximately 50–60% of all cases and representing a major public health concern with significant social and economic impact. Alzheimer's disease (AD) is a neurological disorder and is the most prevalent form of age-related dementia in the modern society. With increasing life expectancy, dementia is a growing socio-economic and medical problem. The number of persons affected by AD in the United States is expected to almost triple

by 2050, reaching 13.8 million (Chintamaneni & Bhaskar, 2012; Rebeiro *et al.,* 2013).

The canine model has a rich literature in psychological and neurobiological research, dating back to the 1800s. Canines are useful for aging research, have moderate lifespans of 12 to 20 years, depending on the breed and are easy to handle due to a long history of domestication. Furthermore, canines are highly motivated to perform consistently on cognitive tests using simple food rewards. Dogs share the same environment with humans. In contrast, mice are not readily cooperative in performing behavioural tasks, so physiological stressors including food restriction, water deprivation and immersion in water are often used. Cognitive dysfunction (CD) is a common manifestation of several neurological and non-neurological conditions of aged dogs and cats. Typical CD signs include disorientation, loss of house training (house soiling) and activity changes (hypo- or hyperactivity). In senior animals these signs may be the effect of a wide variety of medical conditions, behavioural problems, senile cognitive dysfunction (a neurodegenerative disease bearing similarities to Alzheimer's disease of humans) or a combination thereof. Furthermore, behavioural changes are often observed as side effects of common medications (e.g. corticosteroids). Neurological diseases associated with CD include structural encephalopathies, epilepsy, sensory dysfunction (senile visual and/or auditory deficits), peripheral sensory neuropathies. Non-neurological conditions often accompanied by CD signs include endocrine disorders (hypothyroidism, hypoadrenocorticism, hyperadrenocorticism, diabetes mellitus, insulinoma, functional testicular tumours), painful orthopedic (osteoarthritis, polyarthritis, diskospondylitis, bone tumours), gastrointestinal, urogenital and dermatologic diseases.

The pathognomonic AD lesions are the deposition of extracellular amyloid-β (Aβ) plaques surrounded by dystrophic neurites and of arterial walls (CAA) and the presence of intraneuronal neurofibrillary tangles (NFTs) in the hippocampus, cerebral cortex and other areas of the brain important for cognitive function. The third hallmark of brains of dementing patients and aged dogs is loss of synaptic interneuronal connections. Additionally astrocytic gliosis (AG) has been reported in the brain of aged normal human and animals, in patients with AD and senile dementia of the Alzheimer type and in the aged animals (Papaioannou *et al*., 2001; Rofina *et al.,* 2001).

It is well known that plasma Aβ levels have been examined in humans as putative biomarkers for AD, while according to our data, limited similar studies have been conducted for canine dementia. Moreover the diagnostic guidelines of AD have recently been updated to include brain imaging and cerebrospinal fluid (CSF) biomarkers. We try to measure Aβ, the astrocytic marker YKL-40, the ApoE, the APP and the tau protein in the blood, cerebrospinal fluid and saliva of aged canine with or without cognitive dysfunction (Gonzalez-Martinez *et al.,* 2011, Rosen *et al.,* 2013).

It is well known that lipid peroxidation via free radical injury occurs in amyloid deposits of Alzheimer's disease in human patients (Tonnies & Trushina, 2017). Since 4-hydtoxynonenal (HNE), an aldehyde marker of this oxidative injury has been identified in plaques, and inhibitors of free radical formation block *in vitro* toxicity of amyloid β-peptides, amyloid deposits in the tissue may exhibit such toxic effects during their generation proc-

ess. We have detected the presence of oxidative damage in association with plaque formation in the brain of aged dogs. Our results suggest that free radical injury is involved in the pathogenesis of amyloid deposition in canine brains. The decrease of the mean relative arterial brain volume and the increase of HNE staining and of Aβ deposition with aging suggest a relationship between these variables. In dogs meningeal arterial amyloidosis is known to precede the formation of amyloid plaques. According to our results it can be hypothesised that reduced arterial elasticity associated with deposition of amyloid in the cerebral vessel might have favoured episodes of brain ischemia leading to secondary oxidative stress on reperfusion. In turn, this oxidative stress may have stimulated deposition of Aβ protein (Papaioannou *et al.,* 2001).

Another important approach for the etiology of AD is that this may be provoked by a chronic bacterial infection that the patient suffered from. It is probable that bacterial components from the infection remain and circulate in the blood of patients and lead to a progressive neurodegeneration. Our preliminary results indicate positive immunostaining for both bacterial components, flagellin and rhamnolipids (RLs), in the aged human and canine brains. Further experiments are in progress for monitoring the influence of various factors to confirm this impressive result.

All the above lead us to conclude that it is clear that the "One health" concept with the dogma of the catholic approach of medicine is the epitome of modern medicine as the way that we approach clinical conditions and the way they are involved is identical between humans and animals.

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