® Postepy Hig Med Dosw (online), 2013; 67: 269-275
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 2012.09.25
Accepted: 2013.02.21
Published: 2013.04.11

Age-Related Changes in the Central Nervous System in Selected Domestic Mammals and Primates*

Zmiany starcze w ośrodkowym układzie nerwowym u wybranych ssaków udomowionych i naczelnych

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Aging is a process which operates at many levels of physiological, genetic and molecular organization and leads inevitably to death [18]. Brain macroscopic changes by MRI investigation during aging were observed in humans and dogs but chimpanzees did not display significant changes. This suggestion led to the statement that brain aging is different in various species. Although human brain changes, e.g. β-amyloid storage, neurofibrillary tangle formation, lipofuscin, are relatively well known, we are still looking for a suitable animal model to study the mechanisms of aging and neurodegenerative diseases. Therefore, this paper presents a comparative analysis of the changes described in the brains of senile dog, horse and gorilla. In addition we present the latest, non-invasive methods that can be applied in the diagnosis of old age in mammals. Our considerations have shown that the best animal model for further studies and observations on aging is the dog.

Keywords: **aging • brain • mammals • MRI**

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID=1044490

Word count: 3336
Tables: –
Figures: 2
References: 35

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Abbreviations: **Aβ** – β-amyloid; **AD** – Alzheimer disease; **APP** – amyloid protein precursor; **CA** – corpora amylacea; **CAA** – cerebral amyloid angiopathy; **CNS** – central nervous system; **MRI** – magnetic resonance imaging; **MRS** – magnetic resonance spectroscopy; **MT** – microtubule; **NFT** – neurofibrillary tangle; **NMR** – nuclear magnetic resonance; **PAS** – periodic acid Schiff; **PGB** – polyglucosan bodies; **PHF** – paired helical filaments; **SN** – substantia nigra; **SP** – senile plaques

*This work was supported by grant from the National Science Centre of Poland grant N N308578239.

Introduction

Various changes develop with age in the nervous system of man and animals. Lesions such senile plaques, cerebral β-amyloid angiopathy, neurofibrillary tangles, corpora amylacea and mineralization appear with advancing age in the human brain but are not specific to the human brain. In the brains of aged dogs, horses and nonhuman primates similar changes have been reported frequently [30]. These species may therefore serve as animal models for investigating e.g. β-amyloidosis in Alzheimer's disease [35]. However, comparable data on the effects of brain aging in humans and chimpanzees differ from each other in several ways [28]. Therefore we hypothesized that in spite of mutual features in senile brain, there are species-dependent differences between animals and humans. According to us, the knowledge about the differences between species is important to find alternative animal models of human aging to study disability-free longevity, not just the addition of years. For this purpose we monitored morphological neurological changes in brains of dogs (living in the same environment as people), horses (which acquire many of the same diseases that plague humans) and primates (close relatives of humans) to corroborate the usefulness of natural animal models for the study of normal aging and neurodegenerative diseases.

Theories of aging

Biological, epidemiological, and demographic data have generated a number of theories that attempt to identify a cause or process to explain aging and its inevitable consequence, death. However, in recent years, the search for a single cause of aging, such as a single gene or the decline of a key body system, has been replaced by the view of aging as an extremely complex, multifactor process. Several processes may interact simultaneously and may operate at many levels of functional organization [32]. Attempts to classify theories of aging have led to two major categories: programmed aging and wear and tear aging. Programmed aging is aging due to something inside an organism's control mechanisms that forces elderliness and deterioration –similar to the way genes programme other life stages such as cell differentiation during embryological development or sexual maturation at adolescence. By contrast aging due to wear and tear is not the result of any specific controlling programme, but is the result of the sum effect of many kinds of environmental assaults, damage due to radiation, chemical toxins, metal ions, free radicals, hydrolysis, glycation, disulfide-bond cross-linking, etc. For many organs – particularly the brain, heart, lung and kidney – specific disease states associated with aging are of more significance than generalized deterioration. There is wide

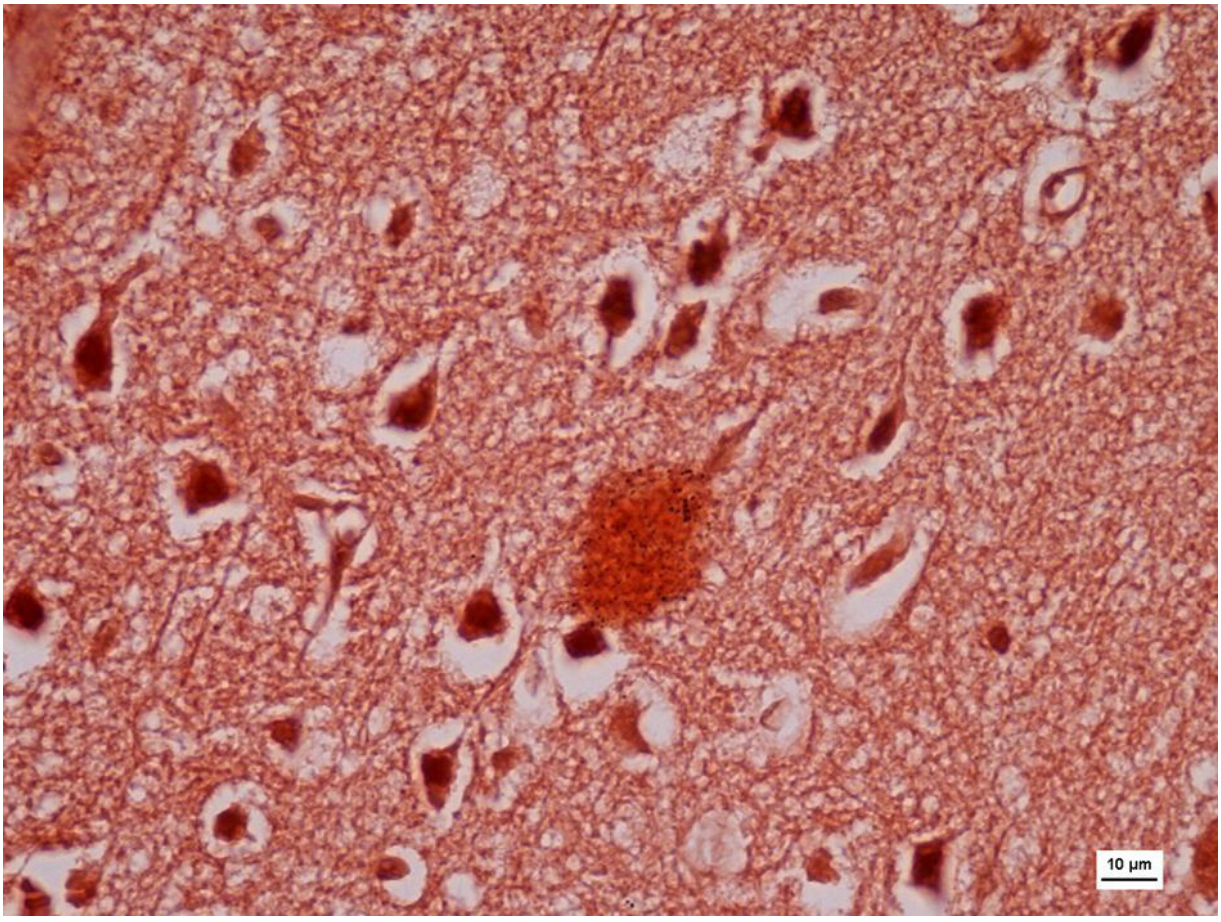

Fig. 1. Brain; 14-month rat, β-amyloid deposition in pyramidal layer of cortex, Congo-red stain (author's own research)

variation in the health status of specific organs among the elderly [1]. In the aging brain many signs of deterioration have been observed. We grouped them, and described the morphological changes below.

Macroscopic changes

Few macroscopic changes were observed in old dogs compared with young controls. Narrowing of gyri and widening of sulci were evident in some of the oldest dogs together with an increase in ventricular volume. These changes are well known in humans but rarely reported in animals. Both cerebral atrophy and ventricular enlargement have been related to the loss of cortical neuronal populations in elderly people. Whether this is also true in animals is unknown, but selective loss of neurons has been described by several authors for a variety of species. Although a quantitative analysis of neuronal loss was not performed, satellitosis and neuronophagia were found in dogs; neuronophagia was a clear indication of neuronal loss [3].

Amyloid (corpora amylacea)

β-amyloid (Aβ) deposition in brain is a progressive age-related process beginning with diffuse deposits of immunologically cross-reacting proteins in the deep cortical layers followed by the development of deposits in other parts of the cortex [26,29,30]. Aβ structure is visible in light microscopy after staining with Congo red, cresyl violet, PAS reaction and by fluorescence and immunofluorescence microscopy [Fig. 1]. The various forms of Aβ are classified biochemically according to the protein precursors. To date, 25 different amyloid protein precursors (APP) have been identified [10]. The extracellular Aβ in brain is generated by enzymatic processing of APP. Overexpression of APP as seen in Down syndrome and induced mutations in transgenic mice may lead to early onset of Alzheimer's disease (AD). Aβ is deposited in the cerebral vessel walls and in the brain cortex as senile plaques (SPs) accumulating on and between the membranes of degenerating neural structures and an abundance of microglia and astrocytes [5,25,26]. Aβ- positive staining was found in the brains of 8.5-year-old dogs and in older dogs revealing vascular staining and plaques. Corpora amylacea (CA) have been observed in an albino gorilla (*Gorilla gorilla gorilla*) throughout the brain but with topographic predilection for the periventricular white matter, hippocampus, medial temporal cortex, medulla oblongata, and, more abundantly, the pars reticulate of the substantia nigra (SN). CA from the SN and hippocampus were smaller than those found in the rest of the gorilla's brain. Most of the CA found in the gorilla had accumulations of ubiquitin and microtubule-associated proteins similar to CA accumulated in human aging. However, CA located principally in the hippocampus and SN in the gorilla were almost all negative to both these proteins and mostly had accumulations of phosphorylated neurofilaments and α-synuclein [16].

Tau and neurofibrillary tangles

Tau is a microtubule [MT]-associated protein stabilizing microtubules as tracks for axonal transport [19]. Neuronal microtubules play a central role in axonal growth and development by providing a structural framework for new axons by serving as substrates for membrane vesicle transport in the axon and stabilize microtubules against depolymerization. In brain, the expression and activity of tau are known to change during development. The immature brain tau proteins are a closely spaced doublet at 48 kDa, while adult brain tau is considerably more heterogeneous, with at least three prominent doublets. Tau appears to be only a single gene from which diversity is generated by both alternative splicing and posttranslational modifications, such as phosphorylation [23,24]. In degenerating neurites hyperphosphorylated cytoskeleton protein, tau and also ubiquitin have been encountered. Both are major components of paired helical filaments (PHF) in AD brains and lead to dementia. Polymerization of tau into PHF and binding of ubiquitin initiate neurofibrillary tangle (NFT) formation. Ubiquitin is a small heat shock protein involved in the degeneration of altered cytoplasmic proteins (target proteins for nonlysosomal ATP-dependent proteolysis). There is increasing concern about the role of ubiquitin in relation to NFTs [26]. Ubiquitin-positive immunoreactions were detected as granules and globules of various sizes in white matter of all old dogs but never in young control dogs. The density of ubiquitinated bodies increased with age. Immunoreactive bodies appeared among axonal fibres and were seen only occasionally in glial cells or neurons. A primary myelin disorder inducing increased levels of abnormal proteins or a decreased proteolytic rate has been proposed to explain the presence of these ubiquitinated bodies [3]. In dogs tau was detected in neurons of the hippocampus and cortex of the parietal lobe. The positivity was located in the cytoplasm as granules and in the axon processes as threads. The positive neurons resembled those in human brains during the early stage of tauopathy [26].

Lipofuscin

Lipopigments are cytoplasmic pigments that have an affinity for neutral lipid stains. They are classified as those that occur normally in tissues (lipofuscin) and those generated experimentally or associated with pathological conditions (ceroid) [8]. Lipofuscin, or age pigment, is an autofluorescent material which accumulates progressively with age within secondary lysosomes in long-lived postmitotic cells of man and animals. For all we know lipofuscin is a conglomerate of lipids, metals (iron, aluminium, copper), organic molecules and biomolecules [4,20]. Typically, lipofuscin stains well with oil red O, Sudan black, acid fast, and PAS stains [Fig. 2]. A variety of studies indicate that lipofuscin formation and accumulation within the lumen of secondary lysosomes is fundamentally linked to the hydrolytic activity within lysosomes. Intracellular digestion of substances taken into

the cell by endocytosis occurs primarily in lysosomes, as does the degradation of molecules and organelles of the cytoplasm constantly targeted and removed by autophagy. Also, lipofuscin-overloaded lysosomes might be unable to further handle peroxidized material formed during oxidative stress, which would increase the intracellular concentration of lipid peroxidation, such as malondialdehyde, impairing critical cellular functions. [2,12]. Intraneuronal lipofuscin deposits were observed also in horses and the quantity of the pigment and the number of areas affected increased with age. In young horses, intraneuronal lipofuscin was largely confined to the mesencephalic trigeminal nucleus, the red nucleus, and the vestibular nucleus. In other equine studies, the olivary nucleus and the pyramidal cells of the cortex were the regions affected in young horses. However, it was suggested that the anatomical distribution of lipofuscin is related to the activity of the nuclei. Age-related glial and neuropil lipofuscin deposition in horses were confined to the rostral part of the brain. Lipofuscin deposition is caused by intracellular accumulation of cell debris after autophagic lysosomal degeneration. Finding this pigment in neuropil may be the result of occasional exocytosis. Another theory is that glial cells containing lipofuscin pigment become pyknotic and die, and afterward only extracellular deposit can be observed [13]. Lipofuscin storage was present in aged dogs, with a wide distribution in cerebral cortex, basal nuclei, thalamus, hippocampal pyramidal neurons, cerebellar dentate nuclei, and some midbrain nuclei. Although lipofuscin in young control dogs appeared as small perinuclear and granular deposits, old dogs had more diffuse granular deposits affecting the pericardia and proximal dendritic tree [3].

Vascular changes

Vascular age-related changes in CNS include: thickening, fibrosis, hyalinosis of small arteries, calcification of the tunica externa of blood vessels and choroid plexus, microhaemorrhages and Aβ in small blood vessels of the cerebral cortex (cerebral amyloid angiopathy). The most prominent change observed in old dogs was fibrosis of the vessel walls. Adventitial thickening showed a focal distribution in most cases, affecting both meningeal and parenchymal (especially thalamic) vessel walls and being more frequent in small-diameter veins than arteries. This change seemed to have a variable age distribution but was more marked in 14- and 15-year-old dogs. Other vascular abnormalities were hyalinosis and microhaemorrhages. Hyalinosis affected the tunica media of some arterioles, but there were no other associated vascular or perivascular lesions. Vascular changes were also observed in gorilla brain and were characterized by thickening, fibrosis and hyalinosis of small arteries. Diffuse microspongiosis,

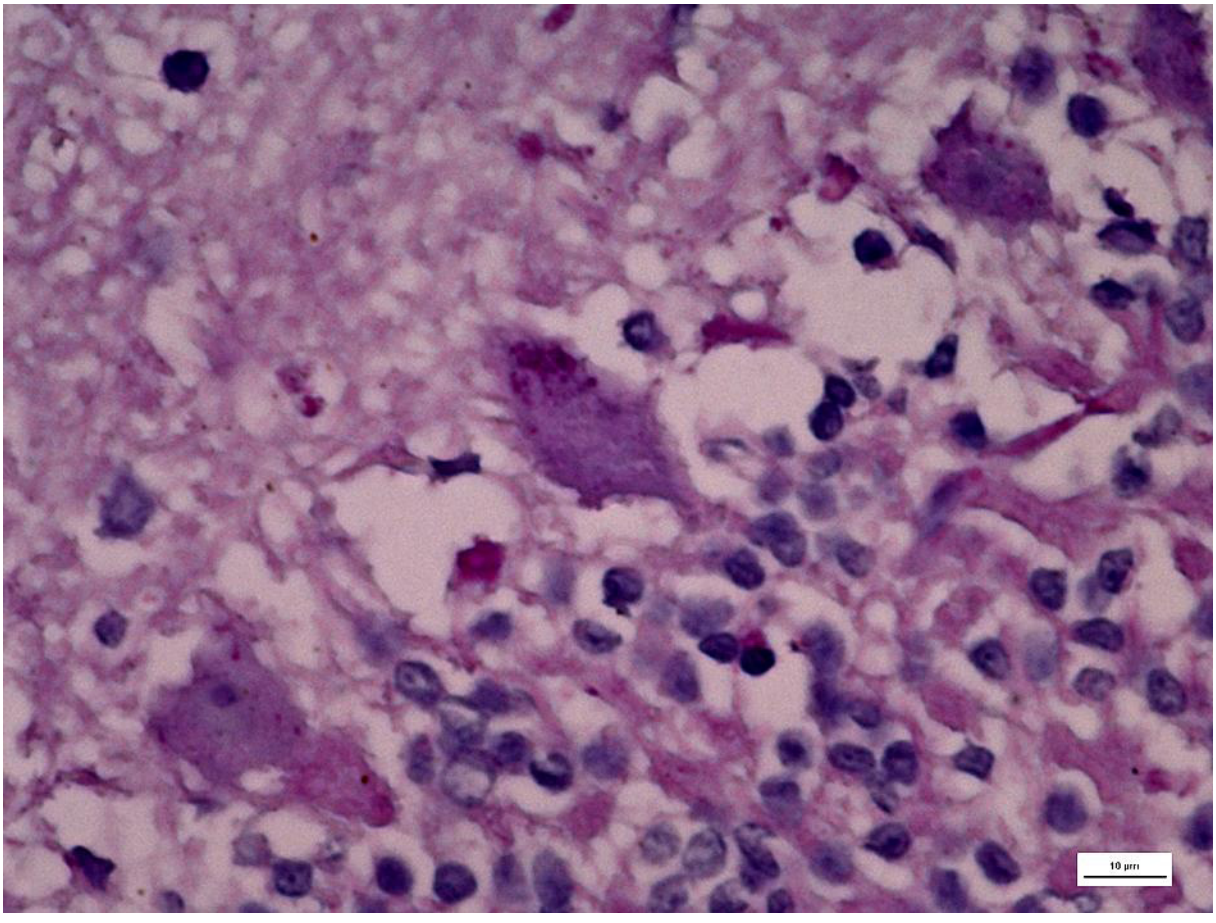

Fig. 2. Brain; 14-month rat, lipofuscin in Purkinje cells of cerebellum, PAS stain (author's own research)

which was more accentuated in perivascular spaces, was observed throughout the nervous parenchyma [16]. The hyalinized vessel walls in brain of horses could not be established. However, age-related vascular changes have been described in humans consisting of thickening of vessel walls, fibrosis and hyalinization [13].

Mineralization in the wall of CNS blood vessels occurs most commonly in aged humans (atherosclerosis), but is also found in animals. In the CNS of aged horses it was observed to affect parenchymal blood vessels, especially in the dentate nuclei and globus pallidus, internal capsule and caudate nucleus, and not to pertain to generalized vascular diseases. In elderly people, a mild degree of calcification inside and around blood vessels is a common incidental finding in the cerebral grey or white matter, without associated symptoms [15]. The morphology and histochemistry of cerebral mineralization in monkeys closely resembled those of human cases commonly found in the globus pallidus. In monkeys no neurological symptoms or signs were recognized, as observed in humans. Because cerebral mineralization induces no clinical signs, it might be physiological rather than pathological, as with mineralization of the pineal gland or choroid plexus currently observed in monkeys. In human Fahr's disease with severe mineralization, lesions of the basal ganglia were observed on radiographs or with computed tomography, showing pathological changes similar to those in mild pallidal vascular mineralization [34].

Cerebrovascular amyloidosis was detected in old dogs, affecting leptomeningeal and parenchymal medium and small calibre arterioles and capillaries. Amyloid protein was also deposited in the external tunica media of vessel walls [35]. Congophilic material was detected in some small blood vessels of the cerebral cortex in gorilla brain [16].

Spheroids

Axonal dystrophy and spheroids are hallmarks of CNS axon pathology [17]. Spheroids were shaped as round or oblong eosinophilic structures of variable size, between 15 μm and 30 μm in diameter, strongly stained with Bielschowsky stain. Immunohistochemical studies showed ubiquitin, α-β-crystallin, tau, and 200 KDa neurofilament accumulation within the spheroids. Perls' method clearly revealed iron deposition in the neuropil and within some spheroids. Increased neuromelanin pigment was also observed in this area. The accumulation of neurofilaments indicates that at least part of the accumulated material inside the spheroids comes from the degraded neuronal cytoskeleton. Tau accumulation in spheroids would indicate an attempt to repair the axonal damage. The α-β-crystallin overexpression in spheroids would protect axons from the aggregation of intermediate filaments and proteins triggered by iron-mediated oxidative stress. The ubiquitin immunostaining of spheroids would indicate activation of the proteolytic nonlysosomal system for the degradation of abnormal filamentous cytoskeletal proteins. Dystrophic axons are usually smaller swellings often associated with continuity of the axon. One or both of these aberrant axon morphologies are found in a wide range of neurodegenerative disorders, including stroke, myelin disorders, tauopathies, amyotrophic lateral sclerosis, traumatic brain injury, AD, Creutzfeldt-Jakob disease, HIV dementia, hereditary spastic paraplegia and Niemann-Pick disease. They also occur during normal ageing and secondarily in some serious illnesses. Moreover, in nonhuman primates, pallido-nigral spheroids associated with iron deposition have been observed in clinically normal gorillas as a normal aging phenomenon [16]. In some instances in horses, the spheroids were associated with coalescing vacuoles in the surrounding grey and white matter, and some spheroids were also vacuolated. Spheroids were common in the brainstem particularly in the nucleus funiculus lat. [13]. In aged dogs spheroids were seen in cerebral grey matter and, more frequently, in cerebral white matter (cortical radiations, corona radiate and capsula interna). Spheroids were negative for neurofilament immunostaining, and only occasional ubiquitin-positive immunoreactions were seen. This differential staining may indicate a different pathogenic mechanism, the former being a consequence of altered axonal retrograde transport and the latter being the result of a defect of normal cellular catabolism [3].

Other changes

Neuronal, neuropil and white matter vacuolation has been reported in the nervous system of a few domestic species [11,13]. In the horse, the main involved areas of neuronal vacuoles were the mesencephalic trigeminal nucleus, the Purkinje cells and the neurons in the raphe at the level of the obex. Neuropil vacuolation contributes significantly to clinically detectable reduced neuronal function and was linked with autolysis, which may predispose brain tissue to artefactual vacuolation. The oculomotor nucleus was the main site affected by neuropil vacuolation in horses. White matter vacuolation in the horses occurred mainly in the internal capsule of the basal ganglia. Vacuolation of white matter has been associated with congenital and acquired degenerative diseases, but the most commonly attributed reasons include hepatic encephalopathy and uraemia, where the vacuolation is distributed at the junction of grey and white matter [13].

Glial changes affected mostly astrocytes. Astrogliosis was seen in old dogs, but astrocytosis (increased number of astrocytes) was observed only in a few dogs. These glial changes were diffuse, bilateral, and more prominent in white than in grey matter, mainly in the corticomedullary junction, corpus callosum, capsula interna, hippocampus, and other cerebellar white matter. Isomorphic gliosis was seen in cerebellar Bergman's glia in old dogs [3]. Gliosis was also seen in horses in the cerebrum and in an aged albino gorilla throughout the nervous parenchyma [13,16].

Polyglucosan bodies (PGB) were detected in many areas, mainly as free neuropil inclusions affecting all aged dogs

but not young controls. The term PGB refers to several different inclusion bodies composed mainly of glucose polymers. Lafora bodies and CA are the two main PGB reported in aged dogs. Ultrastructural canine brain studies have determined the intraneuronal location of Lafora bodies, in both cytoplasm and axons, whereas CA are astrocytic inclusions. Positive ubiquitin immunoreactions have also been described. Lafora bodies may have no overt neurological consequences in aged dogs, but their contribution to cognitive dysfunction syndrome needs more detailed study, especially considering that a disorder similar to Lafora body disease in humans has been described in young dogs, with antecedents of epilepsy, depression, or somnolence [3].

Diagnostic method

Traditional investigations of brain aging were based on histological or immunohistological staining. Today interesting applications which have revolutionised medical diagnosis are MRI and MRS, available for the ante-mortem investigation of various histological types of aging brain. MRI depends on the magnetic properties of some nuclei, most notably the protons in the hydrogen atoms of water, and was developed from its parent technique NMR spectroscopy, which is widely used in chemical analysis. Soft tissue contrast originates mainly in differences in the relaxation properties of the nuclei in different tissues, rather than in the smaller (about 15%) differences in water content [21,22,27]. MRI white matter hyperintensity has been reported in brains of aged dogs as well as in humans. The appearance of white matter hyperintensity is a common manifestation of vascular dementia and is connected with cerebral amyloid angiopathy [6]. We apply this cost-effective MRI technique for investigation of macroscopic age changes in brain which were observed in humans and dogs.

MRS looks back to the analytical role of NMR, but adds spatial localisation, enabling biochemical analysis to be done *in vivo* [21]. The concentrations of most brain metabolites within the neurochemical profile are modified during development, reflecting the structural and functional evolution inherent to the differentiation of cerebral networks. Therefore, the non-invasively detected neurochemical profile may be taken as a marker for specific metabolic states which are associated with degeneration or acute injury. Although brain metabolism has wide differences among species, namely when comparing rodents to humans, once the role of measured neurochemicals is understood, high resolution NMR qualifies as the method of choice for in vivo investigation of preclinical animal models of human neurological and other pathologies during development or aging [7]. 1H-MRS can be used to assess neuronal loss (with the neuronal marker N-acetylaspartate) and thus the progress of neurodegenerative diseases and their response to therapy can be examined [14, 21]. Neurochemical profile detection by 1H-MRS was also carried out in antioxidant defence, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer's disease [7].

Conclusions

In the present study we note that several frequently occurring morphological changes were found in aged brains of dogs, horses and gorillas. Otherwise all changes described in the study are similar to those seen in elderly people suffering from neurodegenerative disease. Already at the beginning of this paper, when analysing macroscopic changes, we drew attention to the similarities of senile brain between man and dog. Further discussed changes such as Aβ and lipofuscin deposition as well as vascular lesions also reflect similarities. Moreover, there are many well-documented physiological similarities between dogs and humans [31]; therefore tapping into the potential of this animal model will add to the existing strengths of conventional model systems. Additionally, it is worth noting that the quality of dogs' lives has improved by enhancing veterinary care and hygiene, and using a proper diet, so the lifespan has increased similarly to human life. Horses and humans have a very similar aging process; both species have a tendency to gain weight as they age, which can result in an imbalance of hormones [33]. But in the case of Aβ deposition in the CNS no changes have been observed by scientific research, so it can be eliminated as an ideal model to study the neurodegeneration process. Monkeys and great apes apparently do not suffer from age-related neuropsychiatric illnesses which occur only in humans, such as AD. The vast majority of morphological studies of brains of aged nonhuman primates indicate that very few changes take place during aging. Importantly, all current studies agree that no decrease in total neuron numbers in the cerebral cortex and in subcortical structures occurs in nonhuman primates [9]. In addition, primates such as gorillas, despite some morphological similarities in development of morphological changes in the brain and close affinity with humans, live in a completely different environment compared to humans and domesticated dogs. Therefore, this also excludes them from the group of animals that may be a perfect model for human senile diseases.

References

[1] Best B.: Mechanisms of Aging. www.benbest.com, (19.09.2012), 1-31

[2] Bildfell R., Matwichuk C., Mitchell S., Ward P.: Neuronal ceroid--lipofuscinosis in a cat. Vet. Pathol., 1995; 32: 485-488

[3] Borras D., Ferrer I., Pumarola M.: Age-related changes in the brain of the dog. Vet. Pathol., 1999; 36: 202-211

[4] Brunk U., Jones C., Sohal R.: A novel hypothesis of lipofuscinogenesis and cellular aging based on interactions between oxidative stress and autophagocytosis. Mut. Research, 1992; 275: 395-403

[5] Castellani R., Lee H., Smith M.: Antioxidant protection and neurodegenerative disease: The role of amyloid-β and tau. Am. J. Alzheimer's and other Dem, 2006; 21: 126-130

[6] Chambers J. K., Uchida K., Nakayama, H.: White matter myelin loss in the brains of aged dogs. Experi. Geronto., 2012; 47: 263-269

[7] Duarte J. M., Lei H., Mlynarik V., Gruetter R.: The neurochemical profile quantified by in vivo H NMR spectroscopy. NeuroImage, 2012; 61:342-362

[8] Edwards J., Storts R., Joyce J., Shelton, J., Menzies C.: Juvenile--onset neuronal ceroid-lipofuscinosis in Rambouillet sheep. Vet. Pathol., 1994; 31: 48-54

[9] Hof P. R., Gilissen E. P., Sherwood C. C., Duan H., Lee H. P.W., Delman B. N., Naidich P.T., Gannon J.P., Perl D.P., Erwin, J. M.: Comparative Neuropathology of Brain Aging in Primates. Aging in Nonhuman Primates., 2002; 31, 130-154

[10] Hirayama K., Miyasho T., Ohmachi T., Watanabe T., Yokota H., Taniyama H.: Biochemical and immunohistochemical characterization of the amyloid in canine amyloid-producing odontogenic tumor. Vet. Pathol., 2010; 47: 915-922

[11] Hooper P. T.: Incidental lesions in the brain of sheep and goats. Aust. Vet. J., 1999; 77: 398-399

[12] Ikeda H., Tauchi H., Sato T.: Fine structural analysis of lipofuscin in various tissues of rats of different ages. Mech. of Age and Develop., 1985; 33: 77-93

[13] Jahns H., Callanan J. J., McElroy C. M., Sammin D. J., Basset H. F.: Age-related and non-age-related changes in 100 surveyed horse brains. Vet Pathol., 2006; 43: 740-750

[14] Lindon C. J., Beckonert O. P., Holmes E., Nicholson J. K.: High-resolution magic angle spinning NMR spectroscopy: Application to biomedical studies. Pro. in Nu. Magne. Resona. Spectro., 2009; 55: 79-100

[15] Mandara M.: Meningial blood vessel calcification in the brain of the cat. Acta Neuropathol., 2003; 105: 240-244

[16] Marquez M., Serafin A., Fernandez-Bellon H., Serrat S., Ferrer--Admetlla A., Bertranpetit J., Ferrer, I., Pumarola M.: Neuropathologic findings in an aged albino gorilla. Vet. Pathol. 2008; 45: 531-537

[17] Mi W., Beirowski B., Gillingwater H. T., Adalbert R., Wagner D., Grumme D., Osaka H., Conforti L., Arnhold S., Addicks K., Wada K., Ribchester R. R., Coleman M. P.: The slow Wallerian degeneration gene, WldS, inhibits axonal spheroid pathology in gracile axonal dystrophy mice. Brain, 2005; 128: 405-416

[18] Miller D., O'Callaghan, J.: Aging, stress and the hippocampus. Aging Res. Rev., 2005; 4: 123-140

[19] Mocanu M.M., Nissen A., Eckermann K., Khlistunova I., Biernat J., Drexler D., Petrova O., Schönig K., Bujard H., Mandelkow E., Zhou L., Rune G., Mandelkow E.M.: The potential for β-structure in the repeat domain of tau protein determines aggregation, synaptic decay, neuronal loss, and coassembly with endogenous tau in inducible mouse models of tauopathy. J. Neurosci., 2008; 28: 737-748

[20] Mochizuki Y., Park M., Mori T., Kawashima S.: The difference in autofluorescence features of lipofuscin between brain and adrenal. Zoological Science. 1995; 12: 283-288

[21] Morris P., Perkins A.: Physics and Medicine 2. Diagnostic imaging. Lancet, 2012; 379: 1525-1533

[22] Motta L., Mandara M. T., Skerritt C. G.: Canine and feline intracranial meningiomas: An updated review. The Vete. J., 2012; 192: 153-165

[23] Oblinger M. M., Argasinski A., Wong J., Kosik K. S.: Tau gene expression in rat sensory neurons during development and regeneration. J. Neurosci, 1991; 11: 2453-2459

[24] Piedrahita D., Hernandez I., Lopez-Tobon A., Fedorov D., Obara B., Manjunath B. S., Boudreau R. L., Davidson B., LaFerla F., Gallego--Gomez J. C., Kosik K. S., Cardona-Gomez G. P.: Silencing of CDK5 reduces neurofibrillary tangles in transgenic Alzheimer's mice. J. Neurosci, 2010; 30: 13966-13976

[25] Puzzo D., Privitera L., Leznik E., Fa M., Staniszewski A., Palmeri A., Arancio O.: Picomolar amyloid-β positively modulates synaptic plasticity and memory in hippocampus. J. Neurosci., 2008; 28: 14537-14545

[26] Rofina J., Singh K., Skoumalova-Vesela A., Ederen A. M., Asten A., Wilhelm J., Gruys E.: Histochemical accumulation of oxidative damage products is associated with Alzheimer-like pathology in the canine. Amyloid: J. Protein Folding Disord., 2004; 11: 90-100

[27] Schmidt J. M., Langen N., Klumpp S., Nasirimanesh F., Shirvanchi P., Ondreka N., Kramer M.: A study of the comparative anatomy of the brain of domestic ruminants using magnetic resonance imaging. Vet. J., 2012; 191: 85-93

[28] Sherwood C. C., Gordon A. D., Allen J. S., Phillips A. K., Erwin J. M., Hof P. R., Hopkins D. W.: Aging of the cerebral cortex differs between humans and chimpanzees. PNAS, 2011; 108: 13029-13034

[29] Takeuchi Y., Uetsuka K., Murayama M., Kikuta F., Takashima A., Doi K., Nakayama H.: Complementary distributions of amyloid-β and neprilysin in the brains of dogs and cats. Vet. Pathol., 2008; 45: 455-466

[30] Uchida K., Yoshino T., Yamaguchi R., Tateyama S., Kimoto Y., Nakayama H., Goto N.: Senile plaques and other senile changes in the brain of an aged American black bear. Vet. Pathol., 1995; 32: 412-414

[31] Waters, D. J. Exploring the pet dog paradigm. Aging Res., 2011; 52(1): 97-105.

[32] Weinert B., Timiras P.: Physiology of Aging, Invited Review: Theories of aging. J. Appl. Physiol., 2003; 95: 1706-1716

[33] Wreiole, M. The horse (*Equus caballus*) as an animal research model for human disease. Animal Models Paper., 2011; 1(14): 1-10

[34] Yanai T., Masegi T., Ueda K., Manabe J., Teranishi M., Takaoka M., Matsunuma M., Fukuda K., Goto N., Fujiwara K.: Vascular mineralization in the monkey brain. Vet. Pathol., 1994; 31: 546-552

[35] Yoshino T., Uchida K., Tateyama S., Yamaguchi R., Nakayama H., Goto N.: A retrospective study of canine senile plaques and cerebral amyloid angiopathy. Vet. Pathol. 1996; 33: 230-234

The authors have no potential conflicts of interest to declare.