Chapter 5

Aging and Neurological Diseases

Marta Kowalska, Michal Owecki, Michal Prendecki, Katarzyna Wize, Joanna Nowakowska, Wojciech Kozubski, Margarita Lianeri and Jolanta Dorszewska

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69499

Abstract

Current knowledge indicates that the aging process starts with subclinical changes at the molecular level. These include the accumulation of mutations, telomere attrition, and epigenetic alterations leading to genomic instability. Such defects multiply exponentially over time, resembling a "snowball effect," and eventually leading to morphological and functional deterioration of the brain, including progressive neuronal loss, reduced levels of neurotransmitters, excessive inflammation, and disrupted integrity of vessels, followed by infarction and microbleeds. Additionally, the decreasing efficiency of DNA repair mechanisms increases the susceptibility to reactive oxygen species and spontaneous mutagenesis, resulting in age-related neoplasia. Moreover, the malnutrition and malabsorption seen commonly in the elderly may cause deficiency of vitamin B_{12} and folic acid, both necessary for homocysteine metabolism, and lead to vascular damage. Altogether, these lead to brain damage in old age and greatly increase the risk of developing diseases of the central nervous system, such as stroke, epilepsy, Parkinson's disease, Alzheimer's disease, and other dementias.

Keywords: aging, molecular factor, neurological diseases

1. Introduction

Physiological aging starts after 60 years of age. Senescence in both animal models and humans is accompanied by alterations in the function of central cholinergic neurons. These changes essentially involve decreased levels of cholinergic receptors, reduced synthesis and release of acetylcholine, and a marked decrease in the number of muscarinic cholinergic neurons, all which may be linked to the age-related memory deficits, a typical change in

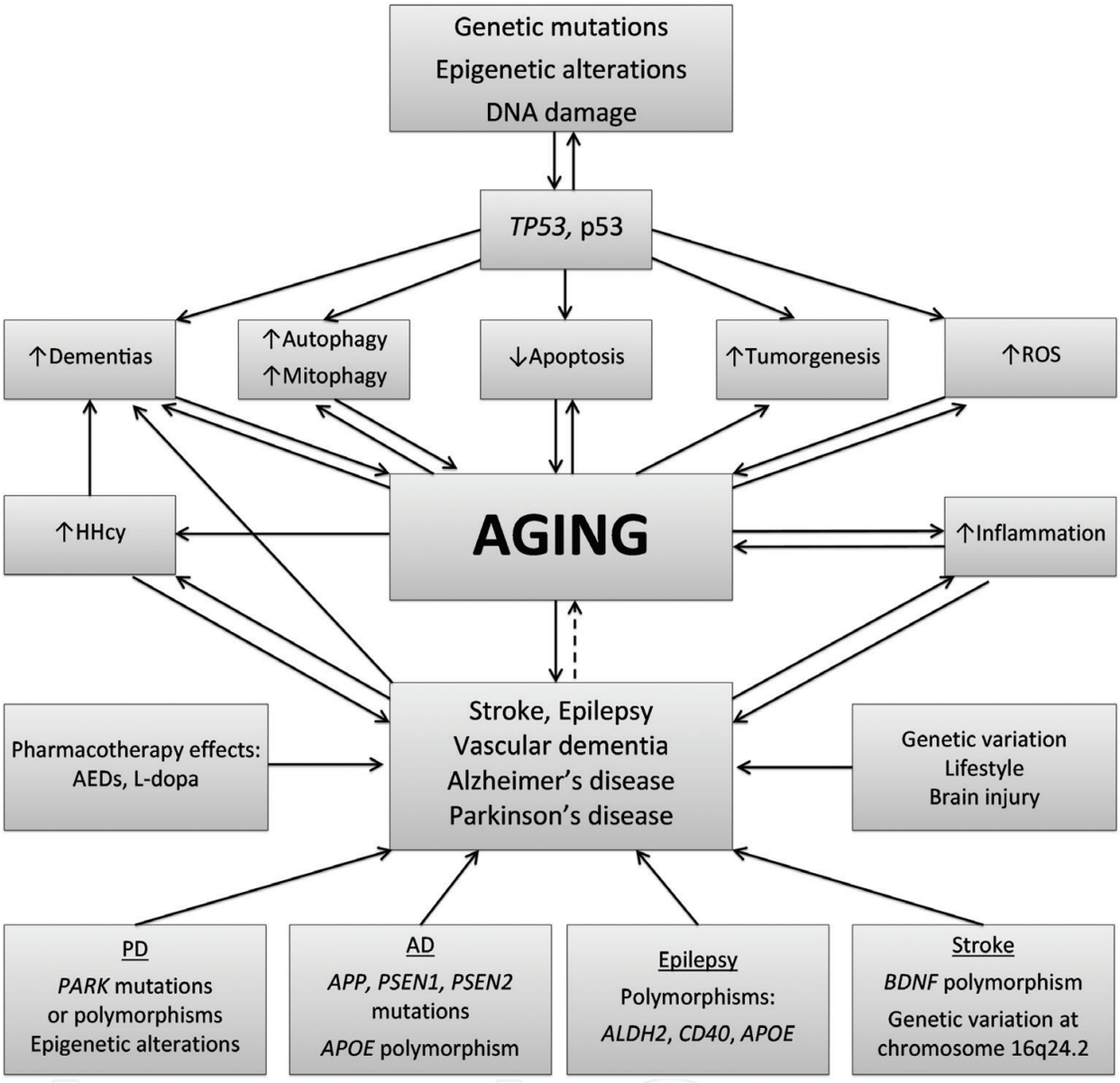

Figure 1. Molecular factors associated with aging and age-related neurological diseases. The pathological changes starting at the molecular level induce oxidative stress and disturb cell cycle that affects cells of the aging organism and lead to systemic deterioration. The genetic variation may give rise to age-related neurological diseases. ROS—reactive oxygen species, HHcy—hyperhomocysteinemia, AEDs—antiepileptic drugs, AD—Alzheimer's disease, and PD—Parkinson's disease.

Alzheimer's disease (AD) patients. Moreover, a decrease in the levels of dopaminergic neurons of up to 40–50% may be observed in the *substantia nigra* and of dopamine in the striatum at the end of the sixth decade of life, which are typical changes seen in patients with Parkinson's disease (PD).

Increased longevity in much of the developed world appears to have lead to higher stroke incidence. Apart from an aging population, there is a significant impact of the growing prevalence of hypertension, diabetes, obesity, and disorders of the cardiovascular system on the increase in the incidence of stroke. The prevalence of these diseases increases with age.

The most common causes of epilepsy in the elderly are vascular changes in the brain (approximately 5%) and degenerative diseases of the central nervous system (CNS) (10–20%). Seizures also occur in patients with AD, demyelinating diseases (multiple sclerosis, or MS), metabolic disorders, as well as in toxic and hormonal disorders, or in individuals with a history of brain injuries or CNS infection.

The mechanisms leading to the development of neurological disorders in the elderly have not been fully elucidated. There are no known mechanisms that regulate cell death in the aging brain. It is not known whether the age of various cells induces the process of apoptosis and other mechanisms of neuronal death, and what factors determine the susceptibility to developing neurological diseases in old age. Understanding the causes of the increased incidence of neurological diseases in the elderly may help in their prevention and improve quality of life in old age (**Figure 1**).

The following review is based on literature search through public databases, such as PubMed and Scopus, with the use of keywords: "aging," "molecular mechanism," "neurological diseases," "stroke," "epilepsy," "vascular dementia," "Alzheimer's disease," "Parkinson's disease," and "brain tumor." Subsequently, the authors selected eligible publications and performed further searches through their references in order to find additional articles. The last search was performed in February 2017.

2. The molecular mechanisms of aging

The molecular mechanisms of aging include genome instability as a consequence of the accumulation of gene mutations, telomere attrition, and epigenetic alterations. Interestingly, instability occurs more frequently in some genome regions than in others. The association and interactions between the above mechanisms lead to the functional decline of aging organisms.

2.1. Aging due to DNA damage

The theory of aging establishes that somatic mutations happen randomly during an organism's lifetime and their accumulation eventually affects key functions such as DNA synthesis, degradation, and repair, consequently causing the "error catastrophe." Genetic damage occurs both in nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) [1, 2]. However, mitochondria have an oxidative environment, due to multiple redox reactions in the electron transport chain, and a less efficient DNA repair system, which results in the accumulation of more damaged mDNA than nDNA [3, 4]. The decreased activity of autophagy and mitophagy may also be responsible for the accumulation of mtDNA mutations and mitochondrial dysfunction during aging [5].

The integrity and stability of DNA may be disrupted both by exogenous factors, such as physical, chemical or biological agents, as well as endogenous factors, including DNA replication errors and reactive oxygen species (ROS) [6]. Most of the damage to DNA occurs during the replication process, and the majority of this damage is corrected by a complex network of DNA repair mechanisms. The mismatch repair (MMR) system provides the fidelity

of replication. The checkpoint response is activated by damage that is unrepaired and leads to cell senescence or death, which may also alter tissue and the homeostasis of the body. The loss of key MMR proteins has been observed during aging. The question becomes: is such deterioration a cause or an effect of senescence [7, 8]?

The cell cycle and repair processes are controlled by tumor protein 53 (p53, encoded by *TP53* gene), which is a pivotal regulator of multiple cellular processes, such as reversible and irreversible cell cycle arrest and senescence. The protein is activated by various stress factors to induce apoptosis or autophagic cell death, depending on the cell category [9]. The initiation of cellular aging is designed to prevent proliferation of damaged cells and tumorigenesis. Two main groups of signals activate p53: DNA damage and oncogenic stress. It has been demonstrated that loss of p53 function occurs in senescent cells, as 50% of human neoplasms possesses a mutated copy of the *TP53* gene [10]. Moreover, the mutations in *TP53* were observed also in age-related dementias, such as AD in both humans and its murine model [11, 12] (**Figure 1**).

2.2. The role of telomeres

Telomere attrition is another molecular mechanism responsible for senescence. Telomeres are a structural component of chromosomes localized at the end of each chromatid. They consist of DNA and telomere binding proteins. Telomere DNA is made up of the sequence 5′-TTAGGG-3′ repeated 150–2000 times [13]. The main functions of telomeres are protection against loss of genetic information during replication and prevention of abnormal recombination, chromosome fusion, or chromosomal degradation by exonucleases [14]. During each cell division, the telomere sequence is shortened by a length of 50–200 base pairs (bp) and the structure of telomeres changes. This biological clock is considered to be one of the main mechanisms determining the number of possible cell divisions. Hayflick's observations [15] on somatic cells specified the maximum number of divisions after which cells stop dividing but remain metabolically active. This maximum number is called the Hayflick limit and varies by tissue type and organism. It is known that a reduction in the number of divisions prevents the accumulation of mutations [16].

2.3. Epigenetics of aging

Epigenetic alterations are another molecular mechanism involved in aging and include DNA methylation and histone modifications [17]. The epigenome becomes deregulated with age. Global levels of DNA methylation decrease with age, and changes in the methylation profile may lead to age-associated immune deficiency [18]. The chemical modification of histones includes acetylation, methylation, phosphorylation, ubiquitination, deamination, citrullination, sumoylation, ADP (adenosine diphosphate) ribosylation, and proline isomerization and lead to changes in histone-DNA or histone-histone interactions [19]. Both changes in the DNA methylation pattern and histone modifications can directly alter chromatin packaging, resulting in different parts of the DNA being exposed to transcriptional factors and results in the expression of different genes. Epigenetic studies have demonstrated progressive changes at the

transcriptomic level associated with aging. The age range of 49–56 years in humans seems to be critical in transcriptional senescence. Changes in gene expression, either their increase or decrease, are a longitudinal and dynamic process [20] (**Figure 1**).

2.4. Aging of the brain

Furthermore, senescence comprises aging of the cerebral white matter (WM) and gray matter (GM), including progressive neuronal loss, decreased levels of neurotransmitters, increased inflammation, disrupted integrity, lesions, infarction, and microbleeds [21]. Aging affects not only neurons but also glial cells (astrocytes, oligodendrocytes, microglia), vascular cells, and the basal lamina matrix and interferes with their functions such as maintaining metabolic and ion homeostasis in the CNS, regulating the cerebral blood flow, impulse conduction, and phagocytosis [22]. During aging, the reduction of WM volume is almost threefold higher (loss of 28% of neurons) than the reduction of GM volume (10% of neurons). Thus, changes in WM may result in behavioral and cognitive decline in the elderly. Additionally, the ability for WM repair has been found to be decreased in older individuals. Changes in WM are observed in diseases, such as stroke, PD, and AD [21].

Multiple molecular changes take place during aging, and these form a vast network of interactions. This makes it nearly impossible to determine if age-related diseases are caused by a snowball effect of senescence, or if the converse is true: that these diseases are the result of individual variability. It seems that both hypotheses may be true, as aging is an important risk factor for diseases such as stroke, epilepsy, PD, AD, and brain tumors, but not a certain causative factor (**Figure 1**).

3. Neurological diseases associated with aging

3.1. Stroke

According to World Health Organization (WHO), stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" [23]. There are two main types of stroke, ischemic and hemorrhagic, which have different pathogenesis.

3.1.1. Ischemic and hemorrhagic stroke

In an ischemic stroke, the blood supply to some brain areas is reduced due to narrowing or complete occlusion of arteries, which leads to dysfunction of this part of the brain tissue. The molecular mechanisms involved in the pathomechanism of ischemic stroke include progressive damage of the blood-brain barrier (BBB) due to loss of integrity, degeneration or death of neurons, glial reaction, and infiltration of immune cells. Ischemic stroke represents 85–90% cases of stroke [24, 25]. Age-related changes in WM are thought to increase the risk for stroke, poststroke death [26], and ischemic injury after stroke [27]. One of the molecular features

of ischemic stroke in the elderly is excitotoxicity due to changes in protein expression (e.g. increase in GLT-1, a transporter for glutamate) and production of ROS. The generation of ROS leads to the death of oligodendrocytes and to the disruption of axons within WM. In the aged brain, the functional decline of mitochondria and antioxidant systems is associated with greater oxidative stress and worsen the WM injury upon ischemia [21].

Hemorrhagic stroke may be caused by cerebral hemorrhage and subarachnoid hemorrhage as a result of damage to the brain's blood vessels by chronic hypertension, cerebral arteriovenous malformation, intracranial aneurysm, disambiguation, cerebral amyloid angiopathy, or drug-induced bleeding. The molecular basis of such a hemorrhage is represented by cytotoxicity of blood, hypermetabolism, excitotoxicity, oxidative stress, and inflammation [28, 29].

3.1.2. Senescence, civilization diseases, and stroke

The American Heart Association has reported that stroke is the fifth cause of death in the United States [30]. The risk factors of stroke are divided into modifiable (e.g. hypertension and other cardiovascular diseases, migraine, diabetes, dyslipidemia, diet, addictions) and unmodifiable (age, sex, race, genetic factors). Among the unmodifiable risk factors, the most important is age [31]. The risk of stroke increases exponentially with age in both men and women. It is estimated that the incidence of stroke doubles with each decade of life after the age of 55 and affects as many as 5% of people over the age of 65 [32]. It is known that the majority of modifiable risk factors, such as hypertension, atrial fibrillation, hyperhomocysteinemia (HHcy), and inflammatory processes (e.g. periodontal disease, infections, increased hs-CRP), are more common in the elderly. The effect of aging on the cardiovascular system is cumulative [33]. Atrial fibrillation occurs in 5% of individuals aged 70 or above and is a cause of one quarter of stroke incidents in patients at the age of 80. The risk of stroke can be decreased by antithrombotic therapies [34].

The serum total homocysteine (Hcy) concentration is another independent risk factor of ischemic stroke in the elderly, as it correlates with thrombosis. The population attributable risk of stroke incidence in high Hcy levels (>17.4 μmol/L) changes with age and was estimated at 21 and 26% for age 40–59 years (men and women, respectively) and at 35 and 37% for individuals over 60 years of age (men and women, respectively) [35]. HHcy (level of Hcy more than 15.0 μmol/L) promotes the development of atherosclerosis. Clinical studies have shown that HHcy has a toxic impact on both the vascular and nervous systems and may be observed not only in stroke but also in PD, mild cognitive impairment (MCI), and epilepsy [36]. Supplementation of folate and vitamin B_{12} is essential in the treatment of HHcy, but folate alone does not reduce the risk of stroke [37].

Two thirds of the population aged over 65 years suffers from hypertension [31]. Hypertension has been proven to increase fourfold the risk of stroke; as the blood pressure increases, so does the probability of suffering stroke. Fortunately, a blood pressure reduction of about 10/5 mmHg decreases the risk of stroke by about 35% [33]. Hypertension is often linked with obesity, abnormalities in lipid profile, and type 2 diabetes. Together, these comorbidities contribute to atherosclerosis and thromboembolic stroke.

Diabetes has been found to have a greater impact in developing stroke in women than in men. Diabetes is a significant independent contributor of stroke in older women [38, 39]. However, the risk of stroke in diabetic patients can be decreased with proper intervention and treatment. The Systolic Hypertension in the Elderly Program has shown that antihypertensive treatment in individuals with diabetes can reduce the risk of stroke by about 20% [40].

Disturbances in the lipid profile should be regularly reviewed and treated as necessary, as they are another contributor to stroke. Independent studies have shown that high levels of total cholesterol (in the 240–270 mg/dL range) [41–43] and triglycerides [44, 45] as well as a low level of high-density lipoproteins (HDL, up to 35 mg/dL) [43, 46, 47] increase the incidence of ischemic stroke. According to the Heart Protection Study, statin therapy in the elderly group can reduce the risk of a first stroke by 29% [48]. Another side of the coin is obesity, defined as body mass index (BMI) >30 kg/m^2, or abdominal obesity, defined by a waist circumference >102 cm (men) and >88 cm (women) [33]. It is known that abdominal obesity is a stronger predictor of stroke than BMI [49].

Moreover, it has been observed that infection with some pathogens may cause acute stroke within a week; these pathogens are *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Helicobacter pylori*, Cytomegalovirus, Epstein-Barr virus, and Herpes simplex virus types I and II. This occurs due to the activation of leukocytes and increased tendency for thrombosis at the site of atherosclerotic plaque. Because of immune deficiencies, the elderly are more susceptible to infections and, therefore, to postinfection complications [33].

It should be mentioned that controlling and regulating the modifiable risk factors is extremely important in stroke prevention. Older people tend to pay more attention to stroke avoidance. Epidemiological studies performed in the USA assumed that, in the last decade, the stroke death rate declined more in subjects after the age of 65 than in the younger population [30].

Stroke is a heterogeneous syndrome, with possible genetic background. Single-gene diseases may cause rare, hereditary disorders for which stroke may be a primary manifestation. Recent studies suggest that common and rare genetic polymorphisms that induce diabetes, hyperlipidemia, or hypertension may activate specific stroke mechanisms causing dangerous angiopathies [50]. For instance, the genetic variation at chromosome 16 (locus q24.2) had been shown to induce small vessel stroke. Traylor et al. using modern GWAS method have found that rare variant rs12445022 in *ZCCHC14* gene may induce small vessels dysfunction, thus greatly increase the risk of stroke [51]. Another interesting genetic factor studied in stroke is a polymorphism in *BDNF* gene (rs6265), which results in amino acid change (Val→Met) in the precursor protein, causing a reduction in brain-derived neurotrophic factor (BDNF) activity, which plays a role in rehabilitation after stroke. The studies show that concentrations of BDNF were decreased in acute ischemic-stroke patients compared to controls. BDNF signaling is dependent on the genetic variation which could affect an individual's response to recovery after stroke. The rs6265 polymorphism may also affect the risk of ischemic stroke, post-stroke outcomes and the efficacy of the various forms of rehabilitation [52] (**Figure 1**).

3.2. Epilepsy

Epilepsy is one of the most common neurological diseases, with approximately 50 million sufferers worldwide. Epilepsy is a collection of somatic, vegetative, and/or mental symptoms, which may be the result of morphological or metabolic changes in the brain. Although the disease has a chronic character and had long been thought to be connected with events in infancy or childhood, epidemiological studies have revealed that there is pronounced incidence of epilepsy in people over 65 years of age [53, 54]. To date, many various causative factors have been associated with epilepsy. However, the etiology of the disease remains unknown in 65–75% of patients [55].

Epilepsy that develops after the age of 60 is symptomatic in the vast majority, although generalized epilepsy may also rarely manifest in the elderly [56]. Epileptic seizures are often underdiagnosed in that age group. The symptoms are usually recognized as memory disorders or mental changes of uncertain origin [57]. Risk factors for epilepsy and seizure etiology vary with age. The most common mechanism of pathogenesis of new-onset epilepsy and seizures in the elderly may be associated with cerebrovascular diseases (CVDs), neuron degenerative disorders, intracerebral tumors, and traumatic head injury [58, 59].

3.2.1. Epilepsy and cerebrovascular diseases

CVDs account for 30–50% of all identified causes of epilepsy in the elderly [60, 61]. Epilepsy attacks may be affected by a stroke and may occur immediately after an ischemic event or be delayed. Seizures may also be the first clinical manifestation of brain ischemia or hemorrhage, increasing the risk to develop epilepsy within the first year after the vascular episode by 20 times. The study of Alberti et al. [62] showed that hemorrhagic transformation of an ischemic stroke is a predictive factor for epilepsy and may also be related to the disruption of the BBB [63]. Numerous genetic factors may be engaged in epileptogenesis. According to Yang et al. [64], mitochondrial aldehyde dehydrogenase 2 (ALDH2, encoded by the *ALDH2* gene) has a protective effect in CVDs. Nevertheless, allele A of the rs671 polymorphism in the *ALDH2* gene was shown to be connected with post-stroke epilepsy due to decreased activity of ALDH2 leading to accumulation of the potential ALDH2 substrate—4-hydroxynonenal (4-HNE), considered to be a specific marker of oxidative stress and involved in myocardial and cerebral ischemia. Zhang et al. [65] suggest that the T allele of the -1C/T polymorphism in the *CD40* gene may be associated with susceptibility to poststroke epilepsy (**Figure 1**). The proposed mechanism includes raised plasma concentrations of sCD40L, which is involved in the inflammatory response. Moreover, poststroke epileptogenesis was shown to be associated with lifestyle factors (alcohol use), acute metabolic disturbances (hyperglycemia), non-CNS comorbidities (type 1 or 2 diabetes, hypertension, coronary heart disease or myocardial infarction, as well as peripheral infections), CNS diseases (early seizures, depression or use of antidepressants, dementia), and pharmacotherapy (statins) [66].

3.2.2. Epilepsy due to head trauma

Another causative factor of epilepsy in the elderly may be head trauma. Due to an increased likelihood of imbalance, older people are more prone to falls causing head injuries. Acute events,

such as skull fractures, subdural hematoma, brain contusion, accidental injury, concussion, or loss of consciousness, were shown to be associated with increased risk of posttraumatic epilepsy [67]. Moreover, various genetic factors were shown to be associated with head injury as a risk factor for late posttraumatic seizures. Diaz-Arrastia et al. [68] showed that carriers of the pathogenic *APOE* E4 allele were more likely to develop epilepsy after suffering acute head trauma (**Figure 1**).

3.2.3. Epilepsy due to brain tumor

Epileptic seizures are common symptoms of brain tumors (BTs) in 20–40% of patients. The study of de Assis et al. [69] demonstrates that BTs related to epilepsy include primary CNS lymphoma, meningioma, anaplastic ependymoma, and anaplastic astrocytoma. The highest incidence of epilepsy occurs in low-grade tumors like primary astrocytoma, oligodendroglioma, mixed astrocytoma WHO grade I and II, as well as meningiomas. It seems that the incidence of seizures is inversely correlated to the grade of the malignancy. Age is a risk factor for increased mortality in those BT patients who develop seizures. Epilepsy attacks also appear in 67% of patients with melanocytic brain metastases, in 48% patients with lung cancer metastases, in 33% patients with breast cancer, and in 55% of patients in whom the primary cancer type was unknown. Unfortunately, BT-related epilepsy is characterized by pharmacological resistance [69, 70].

3.2.4. Biochemical factors in epilepsy

Hcy seems to have additional and interesting significance for the development of epilepsy. As stated earlier, HHcy has demonstrated an association with several disorders, including epilepsy [71]. High Hcy concentration has been shown to be related to numerous factors, including lifestyle (smoking, high consumption of alcohol, caffeine), age (due to the weakening of the excretory function of the kidneys, malabsorption of vitamin B_{12} in the stomach, hormonal disorders, e.g. in women during and after menopause), comorbid diseases, pharmacotherapy (e.g. antidiabetic drugs or fibrates), or unbalanced diet (deficiency of vitamin B_{12} or folic acid) [72–75]. Moreover, Schwaninger et al. [76] demonstrated that prolonged treatment with antiepileptic drugs (AEDs) may increase the plasma concentration of Hcy. On the other hand, the authors were not able to conclude whether the HHcy in epilepsy patients was a sole effect of pharmacotherapy or a causative factor of the disease.

Seizures may also occur in metabolic disorders, because of multiple comorbidities and polypharmacy. There should be a high index of suspicion for electrolyte imbalance, especially hyponatremia and hypoglycemia, in this group of patients. Other metabolic disorders, such as hyperglycemia and uremic or hepatic encephalopathy, are less specific to this age group [77]. The role of alcohol appears to be less important in the elderly than in young adults, but should not be neglected [78], as it may intensify the number of calcium channels and promote seizure activity by increasing the concentration of neurotransmitters [79].

3.2.5. Epilepsy in degenerative diseases

AD is a significant risk factor of epilepsy in the elderly. Imfeld et al. [80] suggested that patients with a longer history of AD (≥3 years) may have a higher risk of developing seizures

or epilepsy than those with a shorter duration of disease. Similar results were presented by Amatniek et al. [81], who observed that the incidence of seizures increased as the disease progressed; the cumulative incidence over 7 years was 8%. The risk of seizure onset is higher in AD patients with hyperlipidemia and severe dementia [82]. The epileptogenetic mechanism has not yet been elucidated in patients with neurodegeneration. It might be associated with β-amyloid (Aβ) deposition, neuronal loss and gliosis, and antidementia drugs [83, 84]. High levels of Aβ are considered a cause of AD, but they are also related to synaptic activity. Aβ serves as a potent regulator of synaptic transmission, causing presynaptic facilitation at relatively low Aβ concentrations and postsynaptic depression with higher Aβ levels. The modulation of synaptic transmission has an important effect on producing epileptiform activity [85].

Another degenerative disorder which may potentially induce seizures is MS, a chronic disease of the CNS. MS usually occurs in young adults (aged 20 to 40 years). However, 1.1–12% of MS patients experience the first symptoms of the disease after the age of 50 [86]. The prevalence of seizures among MS patients was shown to be higher than the general population, which may indicate the relationship between seizures and MS [87]. One possible explanation is that MS lesions act as epileptogenic sites [88]. Generally, a small fraction (2.5%) of MS patients develop seizures [89]. The study of epilepsy in the elderly among MS patients is inconclusive, but clinicians should be aware of the risk of epilepsy in people with MS [88].

3.3. Aging and dementia

Dementia—as a form of cognitive decline—is strongly associated with old age. Almost 10% of those older than 65 years suffer from some kind of memory impairment. The most common causes of dementia include AD and vascular dementia (VaD). The prevalence of dementia increases with age, affecting nearly 50% of the population over 85 years of age. Dementia is a progressive disorder, finally leading to severe disability and complete dependence of sufferers on caregivers [90].

3.3.1. Vascular dementia

VaD was initially understood to be an advanced effect of repetitive brain lesions [91]. The development of brain imaging techniques revealed that silent ischemic lesions appeared to be quite common and later became known as a significant cause of dementia [92, 93]. Epidemiological studies have shown that vascular dysfunction causes 10–20% dementia cases [94, 95]. The frequency of VaD in the general population varies from 1.2 to 4.2% of individuals over 65 years, depending on the methodological approach [94, 96]. The prevalence of VaD is strongly connected with age. A Canadian study described that frequency of vascular cognitive impairment increased from 2.0% in those aged 65 to 74 years to 13.7% in those over 85 years of age [97]. A meta-analysis from 1998, synthesizing the results of 23 studies from around the world, confirmed the trend of increasing incidence of VaD in senescence [98]. Increasing longevity in many populations has also increased the importance and burden of vascular-related memory deficits. A long-term survey demonstrated that the incidence of post-stroke dementia between 1984 and 2001 had doubled [99].

Several studies have analyzed the risk factors, other than age, of CNS vascular lesions. They identified hypertension, heart disease, diabetes with insulin resistance, and dyslipidemia to be related to an increased risk to develop VaD. It is important to note that the results obtained by different authors occasionally contradict each other [100–109]. The cluster of cardiovascular risk factors, also called "metabolic syndrome," that include dyslipidemia, obesity, hypertension, and insulin resistance, has also been shown to be associated with VaD [110, 111]. Additionally, patients with fully symptomatic metabolic syndrome obtained lesser scores in neuropsychological testing [112]. Moreover, HHcy, previously associated with vascular diseases and stroke, was shown to be associated with VaD [113].

Many studies have also demonstrated that a symptomatic stroke incident, occurring mostly in the elderly, may inflict memory deficits in 6 to 32% of patients, depending on the follow-up period (3 months—20 years) [114–128]. MCI preceding stroke increases the probability of post-stroke dementia [129, 130], and memory decline seemed to progress more rapidly with later stroke episodes [131]. Similarly, recurrent stroke was associated with greater cognitive impairment when compared with patients with a single vascular incident [122] (**Figure 1**).

3.3.2. Alzheimer's disease

AD is the most common form of dementia in older adults [132]. AD is a progressive incurable neurodegenerative disease where aging is the primary risk factor. AD may be divided into two main clinical subtypes: familial AD (FAD) characterized by early onset (before 65 years of age) and, frequently, the presence of mutations in the *APP*, *PSEN1*, and *PSEN2* genes. This genetic triad is responsible for nearly half of the FAD cases seen [133]. However, mutations in these genes occur very rarely in the human population. Subsequently, the majority (90%) of AD cases are sporadic (SAD) and manifest mostly in patients over 65 years of age. The multifactorial character of the disease makes it extremely difficult to determine a causative factor for SAD [134]. To date, nearly 700 genes have been associated with AD, although the most investigated risk factor for SAD remains the E4 allele of the *APOE* gene [90, 135, 136].

The diagnosis of probable AD is based on clinical criteria [137], however, the disease may be diagnosed with certainty only after death, by histopathologic study of the brain, revealing characteristic lesions: Aβ plaques and neurofibrillary tangles (NFTs) formed by hyperphosphorylated protein tau. Aβ is formed via pathologic cleavage of (amyloid precursor protein (APP), encoded by the *APP* gene) by β- and γ-secretases (encoded by the *BACE* and *PSEN* genes, respectively). The appearance of Aβ plaques and NFTs seems to be one of the causes for neurodegeneration: the morphological and functional loss of neurons and synapses, as well as excessive neuroinflammatory processes occurring in AD brains. Martin et al. [138] showed that aging and Aβ pathology may activate similar receptors on microglia and monocyte-derived macrophages. Moreover, carriers of the *APOE* E4 allele and rare variants in other genes, such as *HLA-DRB5/DRB1*, *INPP5D*, *MEF2C*, *CR1*, *CLU,* and *TREM2*, may exhibit an even stronger activation of microglia than noncarriers [139]. This explains why older patients with unfavorable genetic variants are more prone to excessive neuroinflammatory responses leading to neuronal loss and dementia.

The neurons mostly affected by AD are cells expressing acetylcholine (ACh) receptors, also called "cholinergic neurons" (AChN). Loss and degeneration of this type of cells is another hallmark of dementia and occurs gradually with age and the course of the disease [140]. The age-related degeneration of AChN leads to decreasing levels of ACh in the brain. ACh has been proven to be the neurotransmitter that is most reduced in the majority of AD patients [141]. It seems that genetic factors, such as the presence of the pathogenic *APOE* E4 allele, may also significantly influence the production and release of ACh. The study on transgenic mice expressing human *APOE* indicated that age-related decrease in ACh levels released by the hippocampus was more prominent in mice with human *APOE* E4/E4 than in mice with *APOE* E3/E3 variants [142] (**Figure 1**).

The main cholinergic structure of the brain is the basal forebrain (BF), the underlying neurodegeneration of which may be observed in advanced aging as well as in the early phase of AD and other dementias [143]. BF degeneration occurs due to a decrease in cholinergic neurotransmission and a reduction in the amount of ACh in synaptic clefts, followed by a loss of cholinergic receptors, finally resulting in AChN death. This process, according to the "cholinergic deficit hypothesis," results in behavioral and cognitive impairment, especially learning difficulties, which advance rapidly with age [144].

It is worth noting that in AD, similarly to VaD and stroke, the concentration of Hcy may be increased and so may inflict damage to the vasculature, thereby leading to decreased blood flow and inefficient nutrient delivery to neurons. Subsequently, the starving cells become more prone to ROS and apoptosis. HHcy is also associated with a decrease of the glutathione pool, the deficiency of which results in the deterioration of protection mechanisms from free radicals, further contributing to neuronal loss and neurodegeneration [145].

3.4. Parkinson's disease and aging

PD is an age-related neurodegenerative disease characterized by resting tremor, rigidity, and bradykinesia. The number of PD patients increases over the years due to population aging. The exact pathomechanism of PD remains unclear, but it is known that the degeneration process starts many years before the occurrence of clinical symptoms. The hallmark of PD is dopaminergic (DA) neuron death in the substantia nigra (SN), which is a result of Lewy body (LB) formation due to impairment of the ubiquitin-proteasome system and disturbances in the proteins alpha-synuclein (ASN) and Parkin [146, 147]. Molecular characteristic of PD include increased ROS production due to mitochondrial dysfunction and accompanied by decreased mitophagy [148], neuroinflammation and loss of neurotrophic factors [149, 150], exposure to (1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP)) or paraquat [151], exposure to trichloroethylene or polychlorinated biphenyls [152], iron (the level of which increase in the SN with age), copper, manganese [153, 154], or mutations in *PARK* genes [155]. Mitochondrial dysfunction is associated with aggregation of ASN, apoptosis, accumulation of damaged mitochondria, and changes in the activity of complex 1 [156]. A decline in mitochondrial function as well as inflammation and changes in DA metabolism are linked with the aging process.

Advancing age is the most important risk factor of developing PD. PD affects about 1% of the population over the age of 60 and 5% over the age of 85 [157]. It has been since 1987 that the loss of DA neurons progresses with aging, but the rate of the physiological process is slower than that seen in PD [158]. Moreover, LB may be present in elderly individuals without PD [159]. The aging brain is also more prone to stressor stimuli and generation of ROS, which results in the injury and eventual death of SN neurons. On the other hand, a decreased level or even loss of ROS scavengers, e.g. neuromelanin, in the PD brain may be a cause of DA neuron damage rather than an effect of this damage [157].

Many epigenetic mechanisms, such as changes in DNA methylation profile and histone modification, play an important role in aging and contribute to PD. The epigenetic clock can be characterized just by measuring the DNA methylation pattern. Interestingly, PD patients represent an increased acceleration in aging when compared to controls of the same age [160]. Hypomethylation of *SNCA*, the gene encoding ASN, leads to an increased expression of ASN and has been observed in the SN of PD patients [161]. ASN can also influence histone acetylation (a feature of transcriptionally active genes) and enhance ASN fibrillation [162].

During normal aging, the functional decline of the BBB can cause neuroinflammation and the development of neurodegenerative diseases [163]. Disturbances in BBB permeability observed in the senescence process may be involved in the genesis of WM lesions, which may also affect the efficacy of treatment. In the course of aggregation of ASN in PD, elevated ROS production and increased levels of proinflammatory cytokines or toxic agents may intensify disruptions of the BBB [164].

HHcy observed in PD may be involved in the disease pathogenesis; however, the exact mechanism of interaction remains unrecognized. Both HHcy and age are risk factors for developing dementia in PD patients [165]. Treatment with L-dopa may be responsible for HHcy in individuals with PD [166]. In those patients, Hcy is formed in the methylation of L-dopa via catechol-O-methyltransferase (COMT) [167]. Other side effects of L-dopa at the molecular level include increased oxidative stress, as well as altered concentrations of catecholamines and apoptotic proteins [147]. Damage of DA neurons due to oxidative stress may be enhanced by elevated Hcy (**Figure 1**). A study performed on mice has shown that elevated Hcy increases the sensitivity to MPTP and developing PD-like dysfunction [168].

3.5. Brain tumors in the elderly

Another type of CNS disease, manifesting particularly in the elderly, are brain tumors, classified according to WHO criteria to four grades, with grade IV considered most malignant [169]. In adults, the most prevalent type of primary brain tumor is malignant glioma (MGs), with the highest incidence between 40 and 65 years of age. The majority of MGs are sporadic, with ionizing radiation as the only known risk factor. The most common type of glioma is glioblastoma multiforme (GBM), qualified as a WHO grade IV astrocytic tumor, and constituting about half of all MGs with the highest incidence in the elderly, between 70 and 90 years of age [170–172]. Old age is a negative prognostic factor in GBM [173]. One of the most significant characteristics of GBM is an increasing prevalence with age; thus, due to an increasing median

length of life, the number of patients is expected to grow in the coming decades. Other types of brain tumors common in the elderly are primary CNS lymphomas (PCNSLs) and meningiomas [174].

GBM comprise a rather heterogenic group of neoplasms, with two major types: primary glioblastomas (85–90%) and secondary GBMs that arise from low-grade astrocytomas (10–15%) [175]. Although both types are indistinguishable under the microscope, they appear to differ genetically. Genetically, primary GBMs exhibit by amplification and mutation of the *EGFR* gene, a lack of heterozygosity on chromosome 10q, inactivation of the *PTEN* homolog gene, and only rare occurrence of mutations in the *IDH* and *TP53* genes. Conversely, the genetics of secondary GBM are characterized by mutations in the *IDH* and/or *TP53* genes, as well as platelet-derived growth factor receptor activation [176]. A gene expression-based GBM classification was established by The Cancer Genome Atlas (TCGA) Research Network in 2010. The authors distinguished four subtypes of GBM. Characteristics that differentiate the subtypes at most were indicated as follows: proneural GBM has alterations of the *PDGFRA* gene and point mutations of *IDH1*, classical GBM has *EGFR* aberrations, and mesenchymal demonstrates GBM aberrations in *NF1*. The fourth subtype, neural GBM, is characterized by the expression of neuron markers such as *NEFL, GABRA1, SYT1*, and *SLC12A5*. Each subtype of GBM differs in its sensitivity to radiotherapy and chemotherapy, thus determining the genetic type of a surgically removed or biopsied lesion could protect patients against unnecessary ineffective therapy [177].

Unfortunately, GBMs are mostly incurable in the elderly, with most of these patients surviving less than 6 months [171]. Diagnosis of primary brain tumors in old age can be further complicated and delayed due to nonspecific symptoms that can be masked by physical and cognitive changes observed in the normal aging process [178]. Moreover, elderly patients are an underrepresented group in many clinical trials [179]. The literature data indicate that, at the close of the twentieth century, the chances of receiving a treatment, be that surgery and/or radiotherapy, were decreasing as the patient got older. Treatment mostly took place for 82% of patients younger than 65 years of age, whereas only 47% of people older than 65 years and merely 25% of patients older than 75 were subjected to any kind of therapy. Additionally, patients treated with radiotherapy and/or surgery had a significantly lower survival rate as they crossed the age border of 60 years [180].

Although pathological processes differ depending on the glioma subtype, there is a common core of molecular events. Growth factor receptor tyrosine kinases cause downstream signaling by activation of extracellular signal-regulated kinases (ERK) or protein kinase B (Akt) pathways. Lack of p53 activation is followed by the loss of the ability to activate DNA repair processes and cell death by apoptosis. An additional adverse characteristic occurring in GBM is that the cells provoke the secretion of vascular endothelial growth factor (VEGF), which is responsible for angiogenesis. The secretion of VEGF by GBM results in vascularization of the tumor, elevation of capillary permeability of the BBB, and creation of extracellular edema [181]. Finally, due to vasculature growth, there is progression of tumor invasion [182].

Although these brain tumors are very invasive, it is important to note that, depending on the tumor subtype, they may be effectively treated in elderly patients by maximally safe surgical resection, radiotherapy, and/or chemotherapy with Temozolomide, a drug which is especially

preferable as first-line treatment in patients with the *MGMT* promoter [179, 183]. In addition to radiotherapy and/or Temozolomide, Bevacizumab (BV, Avastin®) is being studied for the treatment of brain tumors. BV is a humanized IgG1 monoclonal antibody targeting VEGF with high affinity and inactivating the growth factor. Thus, BV promotes tumor regression and helps to decrease the risk of cerebral edema [184]. Interestingly, it has been demonstrated that, although old age is a negative prognostic factor, BV was more effective in older patients (≥55 years of age); those treated with BV remained in better health longer and used lower doses of steroids. These findings were in line with the study published by Nghiemphu et al. [185], who demonstrated that expression of VEGF was 1.4-fold higher in older patients than in younger subjects, and so inhibition of VEGF could give a more positive outcome in these patients.

The increased incidence of brain tumors in the elderly may also be due to decreased efficiency of repair mechanisms. Inactivation of genes involved in DNA repair, such as the above-mentioned *TP53* and *MGMT*, may advance with age. This may lead to increased accumulation of DNA damage, in turn resulting in further activation of proto-oncogenes and silencing of tumor suppressor genes. Such changes, inflicted either by mutation or epigenetic changes, may cause additional destabilization of cellular repair mechanisms, increasing the susceptibility to ROS and spontaneous mutagenesis, and triggering the positive feedback loop of neoplasia [186] (**Figure 1**).

4. Summary

The molecular mechanism of aging includes genome-wide changes such as genomic instability due to accumulation of mutations, telomere attrition, and epigenetic alterations. These changes collect over the years during the life of the organism, leading gradually to morphological and functional deterioration. The brain seems to be particularly vulnerable, as neurons generally do not divide and their pool decreases with the passage of time. Structural changes in the senescent brain affect mostly the cerebral WM and GM; these effects include progressive neuronal loss, decreased levels of neurotransmitters, increased inflammatory processes, and disrupted integrity of vessels and the BBB followed by infarction and microbleeds. These changes may lead to degenerative diseases, such as PD and dementias.

The frequently observed malnutrition and malabsorption syndrome in the elderly may cause decreased concentrations of the vitamins necessary for Hcy metabolism. This in turn results in increased injury to the cerebral vasculature, leading to degeneration and strokes. Consequently, progressive age-related vascular damage of the brain develops, additionally connected to an increased prevalence of epilepsy in the elderly.

An increased incidence of brain tumors may also be observed in old age, probably as an effect of the diminished efficiency of repair mechanisms. The inactivation of genes involved in DNA repair has been shown to advance with age. Such alterations, inflicted either by epigenetic changes or mutation, may cause further destabilization of immunologic systems and cellular repair mechanisms, thus increasing the susceptibility to ROS and spontaneous mutagenesis and resulting in uncontrolled cellular growth and age-related neoplasia (**Figure 2**).

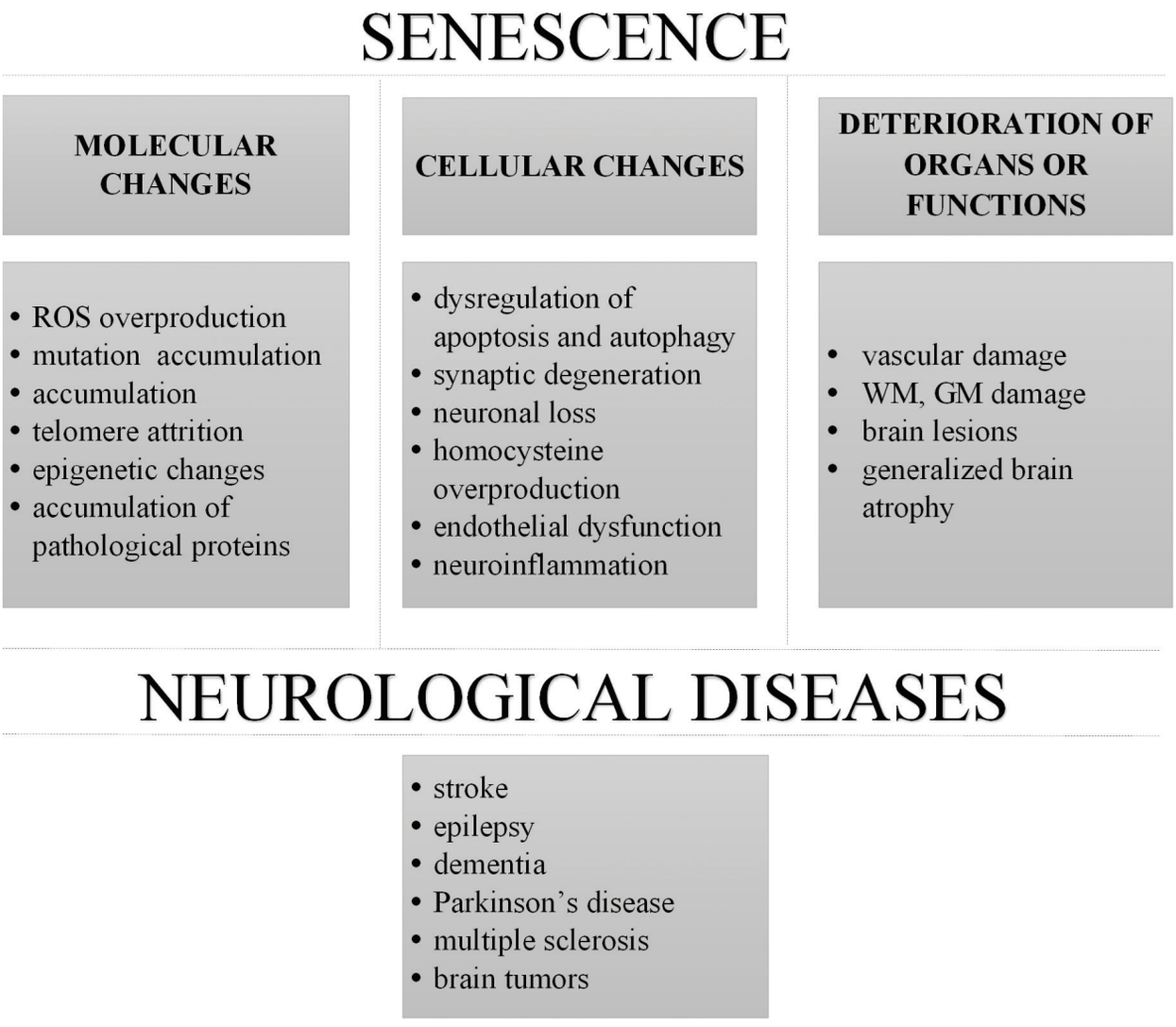

Figure 2. Changes during the senescence process may be associated with neurological diseases. The pathological changes starting at the molecular level affect cells of the aging organism and lead to systemic deterioration, giving rise to age-related neurological diseases. ROS—reactive oxygen species, WM—white matter of the brain, and GM—gray matter of the brain.

In summary, the senescence mechanisms start at a molecular level and gradually lead to morphological disintegration and functional loss of brain cells. Finally, they lead to the deterioration of the CNS and an increased risk of developing neurological diseases.

Acknowledgements

This work was supported by the Poznan University of Medical Sciences grant no. 502-01-11111-45-07-467.

Author details

Marta Kowalska[1], Michal Owecki[1,2], Michal Prendecki[1], Katarzyna Wize[1], Joanna Nowakowska[1], Wojciech Kozubski[3], Margarita Lianeri[1] and Jolanta Dorszewska[1]*

*Address all correspondence to: dorszewskaj@yahoo.com

1 Laboratory of Neurobiology, Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

2 Chair and Department of History of Medical Sciences, Poznan University of Medical Sciences, Poznan, Poland

3 Chair and Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

References

[1] Orgel LE. The maintenance of the accuracy of protein synthesis and its relevance to ageing. Proceedings of the National Academy of Sciences USA. 1963;**49**:517-521

[2] Kirkwood TB. Evolution of ageing. Nature. 1977;**270**:301-304

[3] Blasiak J, Glowacki S, Kauppinen A, Kaarniranta K. Mitochondrial and nuclear DNA damage and repair in age-related macular degeneration. International Journal of Molecular Sciences. 2013;**14**:2996-3010. DOI: 10.3390/ijms14022996

[4] Alexeyev M, Shokolenko I, Wilson G, LeDoux S. The maintenance of mitochondrial DNA integrity- critical analysis and update. Cold Spring Harbor Perspectives in Biology. 2013;**5**:a012641. DOI: 10.1101/cshperspect.a012641

[5] Gaziev AI, Abdullaev S, Podlutsky A. Mitochondrial function and mitochondrial DNA maintenance with advancing age. Biogerontology. 2014;**15**:417-438. DOI: 10.1007/s10522-014-9515-2

[6] Hoeijmakers JH. DNA damage, aging, and cancer. New England Journal of Medicine. 2009;**361**:1475-1485. DOI: 10.1056/NEJMra0804615

[7] Hsieh P, Yamane K. DNA mismatch repair: Molecular mechanism, cancer, and ageing. Mechanisms of Ageing and Development. 2008;**129**:391-407. DOI: 10.1016/j.mad.2008.02.012

[8] Ruzankina Y, Asare A, Brown EJ. Replicative stress, stem cells and aging. Mechanisms of Ageing and Development. 2008;**129**:460-466. DOI: 10.1016/j.mad.2008.03.009

[9] Garcia-Cao I, Garcia-Cao M, Martin-Caballero J, Criado LM, Klatt P, Flores JM, Weill JC, Blasco MA, Serrano M (2002) 'Super p53' mice exhibit enhanced DNA damage response, are tumor resistant and age normally. The EMBO Journal. 2002;**21**:6225-6235

[10] Bougeard G., Brugieres L, Chompret A, Gesta P, Charbonnier F, Valent A, Martin C, Raux G, Feunteun J, Bressac-de Paillerets B, Frébourg T. Screening for TP53 rearrangements in families with the Li-Fraumeni syndrome reveals a complete deletion of the TP53 gene. Oncogene. 2003;**22**:840-846

[11] Dorszewska J, Oczkowska A, Suwalska M, Rozycka A, Florczak-Wyspianska J, Dezor M, Lianeri M, Jagodzinski PP, Kowalczyk MJ, Prendecki M, Kozubski W. Mutations in the exon 7 of Trp53 gene and the level of p53 protein in double transgenic mouse model of Alzheimer's disease. Folia Neuropathologica. 2014;**52**:30-40

[12] Dorszewska, J, Różycka A, Oczkowska A, Florczak-Wyspiańska J, Prendecki M, Dezor M, Postrach I, Jagodzinski P, Kozubski W. Mutations of TP53 gene and oxidative stress in Alzheimer's disease patients. Advances in Alzheimer's Disease. 2014;**3**:24-32. DOI: 10.4236/aad.2014.31004

[13] Lu W, Zhang Y, Liu D, Songyang Z, Wan M. Telomeres-structure, function, and regulation. Experimental Cell Research. 2013;**319**:133-141. DOI: 10.1016/j.yexcr.2012.09.005

[14] Martínez P, Blasco MA. Telomeric and extra-telomeric roles for telomerase and the telomere-binding proteins. Nature Reviews Cancer. 2011;**11**:161-176. DOI: 10.1038/nrc3025

[15] Hayflick L. The limited in vitro lifetime of human diploid cell strains. Experimental Cell Research. 1965;**37**:614-636

[16] Chin L, Artandi SE, Shen Q et al. p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis. Cell. 1999;**97**:527-538. DOI: 10.1016/S0092-8674(00)80762-X

[17] Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes and Development. 2009;**23**:781-783. DOI: 10.1101/gad.1787609

[18] Marttila S, Kananen L, Häyrynen S, Jylhävä J, Nevalainen T, Hervonen A, Jylhä M, Nykter M, Hurme M. Ageing-associated changes in the human DNA methylome: Genomic locations and effects on gene expression. BMC Genomics. 2015;**16**:179. DOI: 10.1186/s12864-015-1381-z

[19] Kouzarides T. Chromatin modifications and their function. Cell. 2007;**128**:693-705. DOI: 10.1016/j.cell.2007.02.005

[20] Irizar H, Goñi J, Alzualde A, Castillo-Triviño T, Olascoaga J, Lopez de Munain A, Otaegui D. Age gene expression and coexpression progressive signatures in peripheral blood leukocytes. Experimental Gerontology. 2015;**72**:50-56. DOI: 10.1016/j.exger.2015.09.003

[21] Liu H, Yang Y, Xia Y, Zhu W, Leak RK, Wei Z, Wang J, Hu X. Aging of cerebral white matter. Ageing Research Reviews. 2017;**34**:64-76. DOI: 10.1016/j.arr.2016.11.006

[22] Cai W, Zhang K, Li P, Zhu L, Xu J, Yang B, Hu X, Lu Z, Chen J. Dysfunction of the neurovascular unit in ischemic stroke and neurodegenerative diseases: An aging effect. Ageing Research Reviews. 2017;**34**:77-87. DOI: 10.1016/j.arr.2016.09.006

[23] Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: Results of a WHO collaborative study. Bull World Health Organ. 1980;**58**:113-130

[24] Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PA, Dennis MS, Warlow CP, Bamford JM, Anslow P. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;**363**:1925-1933. DOI: 10.1016/S0140-6736(04)16405-2

[25] Sohrabji F. Bake S, Lewis DK. Age-related changes in brain support cells: Implications for stroke severity. Neurochemistry International. 2004;**63**:291-301. DOI: 10.1016/j.neuint.2013.06.013

[26] Oksala NK, Oksala A, Pohjasvaara T, Vataja R, Kaste M, Karhunen PJ, Erkinjuntti T. Age related white matter changes predict stroke death in long-term follow-up. Journal of Neurology, Neurosurgery and Psychiatry. 2009;**80**:762-766

[27] Rosenzweig S, Carmichael ST. Age-dependent exacerbation of white matter stroke outcomes: A role for oxidative damage and inflammatory mediators. Stroke. 2013;**44**:2579-2586. DOI: 10.1161/STROKEAHA.113.001796

[28] Smith SD, Eskey CJ. Hemorrhagic stroke. Radiologic Clinics of North America. 2011;**49**:27-45. DOI: 10.1016/j.rcl.2010.07.011

[29] Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: Secondary brain injury. Stroke. 2011;**42**:1781-1786. DOI: 10.1161/STROKEAHA.110.596718

[30] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. American Heart Association Statistics Committee. Stroke Statistics Subcommittee. Executive Summary: Heart Disease and Stroke Statistics-2016 Update: A report from the American Heart Association. Heart Association. Circulation. 2016;**133**:447-454. DOI: 10.1161/CIR.0000000000000366

[31] Strepikowska A, Buciński A. Cerebral stroke—risk factors and prophylaxis. Postępy farmakoterapii. 2009;**65**:46-50. In Polish

[32] Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the 'common' neurologic disorders? Neurology. 2007;**68**:326-337. DOI: 10.1212/01.wnl.0000252807.38124.a3

[33] Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. American Heart Association; American Stroke Association Stroke Council.

Primary prevention of ischemic stroke: A guideline from the American Heart Association/ American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2006;**113**:e873-e923. DOI: 10.1161/01.STR.0000223048.70103.F1

[34] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke. 1991;**22**:983-988. DOI: 10.1161/01.STR.22.8.983

[35] Tanne D, Haim M, Goldbourt U, Boyko V, Doolman R, Adler Y, Brunner D, Behar S, Sela BA. Prospective study of serum homocysteine and risk of ischemic stroke among patients with preexisting coronary heart disease. Stroke. 2003;**34**:632-636. DOI: 10.1161/01.STR.0000060203.58958.35

[36] Ansari R, Mahta A, Mallack E, Luo JJ. Hyperhomocysteinemia and neurologic disorders: A review. Journal of Clinical Neurology. 2014;**10**:281-288. DOI: 10.3988/jcn.2014.10.4.281

[37] Bazzano LA. Folic acid supplementation and cardiovascular disease: The state of the art. American Journal of the Medical Sciences. 2009;**338**:48-49. DOI: 10.1097/ MAJ.0b013e3181aaefd6

[38] Kannel WB, McGee DL. Diabetes and cardiovascular disease: The Framingham Study. Journal of the American Medical Association. 1979;**241**:2035-2038. DOI: 10.1001/ jama.1979.03290450033020

[39] Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. New England Journal of Medicine. 2003;**348**:383-393. DOI: 10.1056/NEJMoa021778

[40] Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. Journal of the American Medical Association. 1996;**276**:1886-1892. Erratum in Journal of the American Medical Association. 1997, **277**:1356. DOI: 10.1001/jama.1996.03540230036032

[41] Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. New England Journal of Medicine. 1989;**320**:904-910. DOI: 10.1056/ NEJM198904063201405

[42] Kagan A, Popper JS, Rhoads GG. Factors related to stroke incidence in Hawaii Japanese men. The Honolulu Heart Study. Stroke. 1980;**11**:14-21. DOI: 10.1161/01.STR.11.1.14

[43] Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinoren OP. Different risk factors for different stroke subtypes: Association of blood pressure, cholesterol, and antioxidants. Stroke. 1999;**30**:2535-2540. DOI: 10.1161/01.STR.30.12.2535

[44] Gordon T, Kannel WB, Castelli WP, Dawber TR. Lipoproteins, cardiovascular disease, and death. The Framingham Study. Archives of Internal Medicine. 1981;**141**:1128-1131. DOI: 10.1001/archinte.1981.00340090024008

[45] Lindenstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: The Copenhagen City Heart Study. British Medical Journal. 1994;**309**:11-15. Erratum in British Medical Journal. 1994, **309**:1619

[46] Wannamethee SG, Shaper AG, Ebrahim S. HDL-cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. Stroke. 2000;**31**:1882-1888. DOI: 10.1161/01.STR.31.8.1882

[47] Soyama Y, Miura K, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Kagamimori S, Nakagawa H. Oyabe Study. High-density lipoprotein cholesterol and risk of stroke in Japanese men and women: The Oyabe Study. Stroke. 2003;**34**:863-868. DOI: 10.1161/01.STR.0000060869.34009.38

[48] Collins R, Armitage J, Parish S, Sleight P, Peto R. Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;**363**:757-767. DOI: 10.1016/S0140-6736(04)15690-0

[49] Isozumi K. Obesity as a risk factor for cerebrovascular disease. Keio Journal of Medicine. 2004;**53**:7-11. DOI: 10.2302/kjm.53.7

[50] Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. Circulation Research. 2017;**120**:472-495. DOI: 10.1161/CIRCRESAHA.116.308398.

[51] Traylor M, Malik R, Nalls MA, Cotlarciuc I, Radmanesh F, Thorleifsson G, Hanscombe KB, Langefeld C, Saleheen D, Rost N, Yet I, Spector TD, Bell JT, Hannon E, Mill J, Chauhan G, Debette S, Bis JC, Longstreth WT Jr, Ikram MA, Launer LJ, Seshadri S. METASTROKE, UK Young Lacunar DNA Study, NINDS Stroke Genetics Network, Neurology Working Group of the CHARGE Consortium, Hamilton-Bruce MA, Jimenez-Conde J, Cole JW, Schmidt R, Słowik A, Lemmens R, Lindgren A, Melander O, Grewal RP, Sacco RL, Rundek T, Rexrode K, Arnett DK, Johnson JA, Benavente OR, Wassertheil-Smoller S, Lee JM, Pulit SL, Wong Q, Rich SS, de Bakker PI, McArdle PF, Woo D, Anderson CD, Xu H, Heitsch L, Fornage M, Jern C, Stefansson K, Thorsteinsdottir U, Gretarsdottir S, Lewis CM, Sharma P, Sudlow CL, Rothwell PM, Boncoraglio GB, Thijs V, Levi C, Meschia JF, Rosand J, Kittner SJ, Mitchell BD, Dichgans M, Worrall BB, Markus HS. International Stroke Genetics Consortium. Genetic variation at 16q24.2 is associated with small vessel stroke. Annals of Neurology. 2017;**81**:383-394. DOI: 10.1002/ana.24840

[52] Kotlęga D, Peda B, Zembroń-Łacny A, Gołąb-Janowska M, Nowacki P. The role of brain-derived neurotrophic factor and its single nucleotide polymorphisms in stroke patients. Neurologia i Neurochirurgia Polska. 2017;**S0028-S3843**(16):30237-7. DOI: 10.1016/j.pjnns.2017.02.008. [Epub ahead of print]

[53] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993;**34**:453-468

[54] Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: A prospective study. Lancet Neurology. 2005;**4**:627-634. DOI: 10.1016/S1474-4422(05)70172-1

[55] Jędrzejczak J. Epilepsy. The hardest are the answers to simple questions. Termedia, Poznań; 2008; 6-11. Book In Polish

[56] Fernandez-Torre JL, Rebollo M. Typical absence status epilepticus as late presentation of idiopathic generalised epilepsy in an elderly patient. Seizure. 2009;**18**:82-83. DOI: 10.1016/j.seizure.2008.08.005

[57] Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. Neurology. 2004;**62**:24-29

[58] Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. Journal of the American Geriatrics Society. 2009;**57**:237-242. DOI: 10.1111/j.1532-5415.2008.02124.x

[59] Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet. 2000;**355**:1441-1446. DOI: 10.1016/S0140-6736(00)02149-8

[60] Tanaka A, Akamatsu N, Shouzaki T, Toyota T, Yamano M, Nakagawa M, Tsuji S. Clinical characteristics and treatment responses in new-onset epilepsy in the elderly. Seizure. 2013;**22**:772-775. DOI: 10.1016/j.seizure.2013.06.005

[61] Assis TM, Bacellar A, Costa G, Nascimento OJ. Mortality predictors of epilepsy and epileptic seizures among hospitalized elderly. Arquivos de Neuro-psiquiatria. 2015;**73**:510-515. DOI: 10.1590/0004-282X20150043

[62] Alberti A, Paciaroni M, Caso V, Venti M, Palmerini F, Agnelli G. Early seizures in patients with acute stroke: Frequency, predictive factors, and effect on clinical outcome. Vascular Health Risk Management. 2008;**4**:715-720

[63] Renu A, Amaro S, Laredo C, Román LS, Llull L, Lopez A, Urra X, Blasco J, Oleaga L, Chamorro Á. Relevance of blood-brain barrier disruption after endovascular treatment of ischemic stroke: Dual-energy computed tomographic study. Stroke. 2015;**46**:673-679. DOI: 10.1161/STROKEAHA.114.008147

[64] Yang H, Song Z, Yang GP, Zhang BK, Chen M, Wu T, Guo R. The ALDH2 rs671 polymorphism affects poststroke epilepsy susceptibility and plasma 4-HNE levels. PLoS One. 2014;**10**:e109634. DOI: 10.1371/journal.pone.0109634

[65] Zhang B, Chen M, Yang H, Wu T, Song C, Guo R. Evidence for involvement of the CD40/CD40L system in poststroke epilepsy. Neuroscience Letters. 2014;**567**:6-10. DOI: 10.1016/j.neulet.2014.03.003

[66] Pitkänen A, Roivainen R, Lukasiuk K. Development of epilepsy after ischaemic stroke. Lancet Neurology. 2006;**15**:185-197. DOI: 10.1016/S1474-4422(15)00248-3

[67] Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. New England Journal of Medicine. 1998;**338**:20-24. DOI: 10.1056/NEJM199801013380104

[68] Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, Agostini MA, Van Ness PC. Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon4 allele. Archives of Neurology. 2003;**60**:818-822. DOI: 10.1001/archneur.60.6.818

[69] Assis TR, Bacellar A, Costa G, Nascimento OJ. Etiological prevalence of epilepsy and epileptic seizures in hospitalized elderly in a Brazilian tertiary center-Salvador—Brazil. Arquivos de Neuro-psiquiatria. 2015;**73**:83-89. DOI: 10.1590/0004-282X20140217

[70] Maschio M. Brain tumor-related epilepsy. Current Neuropharmacology. 2012;**10**:124-133. DOI: 10.2174/157015912800604470

[71] Petras M, Tatarkova Z, Kovalska M, Mokra D, Dobrota D, Lehotsky J, Drgova A. Hyperhomocysteinemia as a risk factor for the neuronal system disorders. Journal of Physiology and Pharmacology: An official Journal of the Polish Physiological Society. 2014;**65**:15-23

[72] Marszałł ML, Makarowski R, Hinc S, Kłos M, Czarnowski W. Hyperhomocysteinemia in active and passive smokers and the levels of folate and vitamin B6 in plasma. Przegląd Lekarski. 2008;**65**:486-490. In Polish

[73] Cravo ML, Camilo ME. Hyperhomocysteinemia in chronic alcoholism: relations to folic acid and vitamins B(6) and B(12) status. Nutrition. 2000;**16**:296-302

[74] Tomaszewski J, Pieprzowska-Białek A, Skorupski P, Rechberger T. Elevated serum homocysteine concentration in women taking oral hormone replacement therapy. Przegląd Menopauzalny. 2003;**5**:31-34. In Polish

[75] Dorszewska J, Winczewska-Wiktor A, Sniezawska A, Kaczmarek I, Steinborn B. Homocysteine and asymmetric dimethylarginine (ADMA) in epilepsy. Przegląd Lekarski. 2009, **8**:448-452. In Polish

[76] Schwaninger M, Ringleb P, Winter R, Kohl B, Fiehn W, Rieser PA, Walter-Sack I. Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. Epilepsia. 1999, **40**:345-350

[77] Ghosh S, Jehi LE. New-onset epilepsy in the elderly: Challenges for the internist. Cleveland Clinic Journal of Medicine. 2014;**81**:490-498. DOI: 10.3949/ccjm.81a.13148

[78] Krämer G. Epilepsy in the Elderly: Some clinical and pharmacotherapeutic aspects. Epilepsia. 2001;**42**:55-59

[79] N'Gouemo P. Altered voltage-gated calcium channels in rat inferior colliculus neurons contribute to alcohol withdrawal seizures. European Neuropsychopharmacology. 2015;**25**:1342-1352. DOI: 10.1016/j.euroneuro.2015.04.008

[80] Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: A population-based nested case-control analysis. Epilepsia. 2013;**54**:700-707. DOI: 10.1111/epi.12045

[81] Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, Albert M, Brandt J, Stern Y. Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia. 2006;**47**:867-872

[82] Bernardi S, Scaldaferri N, Vanacore N, Trebbastoni A, Francia A, D'Amico A, Prencipe M. Seizures in Alzheimer's disease: A retrospective study of a cohort of outpatients. Epileptic Disorders. 2010;**12**:16-21. DOI: 10.1684/epd.2010.0290

[83] Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: Frequency, seizure types, and treatment outcome. Epilepsy & Behavior. 2009;**14**:118-120. DOI: 10.1016/j.yebeh.2008.08.012

[84] Irizarry MC, Jin S, He F, Emond JA, Raman R, Thomas RG, Sano M, Quinn JF, Tariot PN, Galasko DR, Ishihara LS, Weil JG, Aisen PS. Incidence of new-onset seizures in mild to moderate Alzheimer disease. Archives of Neurology. 2012;**69**:368-372. DOI: 10.1001/archneurol.2011.830

[85] Roberson ED, Hope OA, Martin RC, Schmidt D. Geriatric epilepsy: Research and clinical directions for the future. Epilepsy & Behavior. 2011;**22**:103-111. DOI: 10.1016/j.yebeh.2011.04.005

[86] Etemadifar M, Abtahi SH, Minagar A, Akbari M, Masaeli A, Tabrizi N. Late-onset multiple sclerosis in Isfahan, Iran. Archives of Iran Medicine. 2012;**15**:596-598. DOI: 0121510/AIM.004

[87] Sponsler JL, Kendrick-Adey AC. Seizures as a manifestation of multiple sclerosis. Epileptic Disorders. 2011;**13**:401-410. DOI: 10.1684/epd.2011.0468

[88] Allen AN, Seminog OO, Goldacre MJ. Association between multiple sclerosis and epilepsy: Large population-based record-linkage studies. BMC Neurology. 2013;**13**:189. DOI: 10.1186/1471-2377-13-189

[89] Viveiros CD, Alvarenga RM. Prevalence of epilepsy in a case series of multiple sclerosis patients. Arquivos de Neuro-Psiquiatria. 2010;**68**:731-736

[90] Dorszewska J, Prendecki M, Oczkowska A, Dezor M, Kozubski W. Molecular basis of familial and sporadic Alzheimer's disease. Current Alzheimer Research. 2016;**13**:952-963. DOI: 10.2174/1567205013666160314150501

[91] Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet. 1974;**2**:207-210

[92] Hachinski VC, Bowler JV. Vascular dementia. Neurology. 1993;**43**:2159-2160

[93] O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST. Vascular cognitive impairment. Lancet Neurology. 2003;**2**:89-98. DOI: 10.1016/S1474-4422(03)00305-3

[94] Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;**54**:S4-S9

[95] Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, Lobo A, Martinez-Lage J, Soininen H, Hofman A. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;**54**:S10-S15

[96] Hébert R, Brayne C. Epidemiology of vascular dementia. Neuroepidemiology. 1995; **14**:240-257

[97] Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology. 2000;**54**:447-451

[98] Jorm AF, Jolley D. The incidence of dementia: A meta-analysis. Neurology. 1998;**51**:728-733

[99] Ukraintseva S, Sloan F, Arbeev K, Yashin A. Increasing rates of dementia at time of declining mortality from stroke. Stroke. 2006;**37**:1155-115915. DOI: 10.1161/01.STR.0000217971.88034.e9

[100] Hébert R, Lindsay J, Verreault R, Rockwood K, Hill G, Dubois MF. Vascular dementia: Incidence and risk factors in the Canadian study of health and aging. Stroke. 2000;**31**:1487-1493. DOI: 10.1161/01.STR.31.7.1487

[101] Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, Kawas C, Breitner JC, Fitzpatrick A, Dulberg C. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. Neurology. 2005;**64**:1548-1582

[102] Suryadevara V, Storey SG, Aronow WS, Ahn C. Association of abnormal serum lipids in elderly persons with atherosclerotic vascular disease and dementia, atherosclerotic vascular disease without dementia, dementia without atherosclerotic vascular disease, and no dementia or atherosclerotic vascular disease. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2003;**58**:M859-M861

[103] Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Archives of Neurology. 2004;**61**:705-714. DOI: 10.1001/archneur.61.5.705

[104] Posner HB, Tang MX, Luchsinger J, Antigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology. 2002;**58**:1175-1181

[105] Ross GW, Petrovitch H, White LR, Masaki KH, Li CY, Curb JD, Yano K, Rodriguez BL, Foley DJ, Blanchette PL, Havlik R. Characterization of risk factors for vascular dementia: The Honolulu-Asia Aging Study. Neurology. 1999;**53**:337-343

[106] Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia. 1996;**39**:1392-1397

[107] Geroldi C, Frisoni GB, Paolisso G, Bandinelli S, Lamponi M, Abbatecola AM, Zanetti O, Guralnik JM, Ferrucci L. Insulin resistance in cognitive impairment: the InCHIANTI study. Archives of Neurology. 2005;**62**:1067-1072. DOI: 10.1001/archneur.62.7.1067

[108] Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, Sulkava R, Kivipelto M. Diabetes, Alzheimer disease, and vascular dementia: A population-based neuropathologic study. Neurology. 2010'**75**:1195-1202. DOI: 10.1212/WNL.0b013e3181f4d7f8

[109] Dichgans M, Zietemann V. Prevention of vascular cognitive impairment. Stroke. 2012;**43**:3137-3146. DOI: 10.1161/STROKEAHA.112.651778

[110] Kalmijn S, Foley D, White L, Burchfiel CM, Curb JD, Petrovitch H, Ross GW, Havlik RJ, Launer LJ. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;**20**:2255-2260. DOI: 10.1161/01.ATV.20.10.2255

[111] Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Vendemiale G, Baldereschi M, Crepaldi G, Di Carlo A, Galluzzo L, Gandin C, Inzitari D, Maggi S, Capurso A, Panza F. Italian Longitudinal Study on Ageing Working Group. Metabolic syndrome and the risk of vascular dementia: The Italian Longitudinal Study on Ageing. Journal of Neurology, Neurosurgery and Psychiatry. 2010;**81**:433-440. DOI: 10.1136/jnnp.2009.181743

[112] Segura B, Jurado MA, Freixenet N, Albuin C, Muniesa J, Junqué C. Mental slowness and executive dysfunctions in patients with metabolic syndrome. Neuroscience Letters. 2009;**462**:49-53. DOI: 10.1016/j.neulet.2009.06.071

[113] Newman GC, Bang H, Hussain SI, Toole JF. Association of diabetes, homocysteine, and HDL with cognition and disability after stroke. Neurology. 2007;**69**:2054-2062

[114] Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, Wolf PA. Dementia after stroke: The Framingham Study. Stroke. 2004;**35**:1264-1268. DOI: 10.1161/01.STR.0000127810.92616.78

[115] Desmond DW, Moroney JT, Sano M, Stern Y. Incidence of dementia after ischemic stroke: Results of a longitudinal study. Stroke. 2002;**33**:2254-2260. DOI: 10.1161/01.STR.0000028235.91778.95

[116] Altieri M, Di Piero V, Pasquini M, Gasparini M, Vanacore N, Vicenzini E, Lenzi GL. Delayed poststroke dementia: a 4-year follow-up study. Neurology. 2004;**62**:2193-2197

[117] Lin JH, Lin RT, Tai CT, Hsieh CL, Hsiao SF, Liu CK. Prediction of poststroke dementia. Neurology. 2003;**61**:343-348

[118] Censori B, Manara O, Agostinis C, Camerlingo M, Casto L, Galavotti B, Partziguian T, Servalli MC, Cesana B, Belloni G, Mamoli A. Dementia after first stroke. Stroke. 1996;**27**:1205-1210. DOI: 10.1161/01.STR.27.7.1205

[119] Inzitari D, Di Carlo A, Pracucci G, Lamassa M, Vanni P, Romanelli M, Spolveri S, Adriani P, Meucci I, Landini G, Ghetti A. Incidence and determinants of poststroke dementia as defined by an informant interview method in a hospital-based stroke registry. Stroke. 1998;**29**:2087-2093. DOI: 10.1161/01.STR.29.10.2087

[120] Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. Clinical determinants of poststroke dementia. Stroke. 1998;**29**:75-81. DOI: 10.1161/01.STR.29.1.75

[121] Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: A population-based study in Rochester, Minnesota (1960-1984). Neurology. 1996;**46**:154-159

[122] Srikanth VK, Quinn SJ, Donnan GA, Saling MM, Thrift AG. Long-term cognitive transitions, rates of cognitive change, and predictors of incident dementia in a population-based first-ever stroke cohort. Stroke. 2006;**37**:2479-2483. DOI: 10.1161/01.STR.0000239666.46828.d7

[123] Leys D, Hénon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurology. 2005;**4**:752-759. DOI: 10.1016/S1474-4422(05)70221-0

[124] Melkas S, Oksala NK, Jokinen H, Pohjasvaara T, Vataja R, Oksala A, Kaste M, Karhunen PJ, Erkinjuntti T. Poststroke dementia predicts poor survival in long-term follow-up: Influence of prestroke cognitive decline and previous stroke. Journal of Neurology, Neurosurgery, and Psychiatry. 2009;**80**:865-870. DOI: 10.1136/jnnp.2008.166603

[125] Gottesman RF, Hillis AE. Predictors and assessment of cognitive dysfunction resulting from ischaemic stroke. Lancet Neurology. 2010;**9**:895-905. DOI: 10.1016/S1474-4422(10)70164-2

[126] Béjot Y, Aboa-Eboulé C, Durier J, Rouaud O, Jacquin A, Ponavoy E, Richard D, Moreau T, Giroud M. Prevalence of early dementia after first-ever stroke: A 24-year population-based study. Stroke. 2011;**42**:607-612. DOI: 10.1161/STROKEAHA.110.595553

[127] Dong Y, Venketasubramanian N, Chan BP, Sharma VK, Slavin MJ, Collinson SL, Sachdev P, Chan YH, Chen CL. Brief screening tests during acute admission in patients with mild stroke are predictive of vascular cognitive impairment 3-6 months after stroke. Journal of Neurology Neurosurgery, and Psychiatry. 2012;**83**:580-585. DOI: 10.1136/jnnp-2011-302070

[128] Rist PM, Chalmers J, Arima H, Sharma VK, Slavin MJ, Collinson SL, Sachdev P, Chan YH, Chen CL. Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. Stroke. 2013;**44**:1790-1795. DOI: 10.1136/jnnp-2011-302070

[129] Gamaldo A, Moghekar A, Kilada S, Resnick SM, Zonderman AB, O'Brien R. Effect of a clinical stroke on the risk of dementia in a prospective cohort. Neurology. 2006;**67**:1363-1369. DOI: 10.1212/01.wnl.0000240285.89067.3f

[130] Narasimhalu K, Ang S, De Silva DA, Wong MC, Chang HM, Chia KS, Auchus AP, Chen C. Severity of CIND and MCI predict incidence of dementia in an ischemic stroke cohort. Neurology. 2009;**73**:1866-1872. DOI: 10.1212/WNL.0b013e3181c3fcb7

[131] Wang Q, Capistrant BD, Ehntholt A, Glymour MM. Long-term rate of change in memory functioning before and after stroke onset. Stroke. 2012;**43**:2561-2566. DOI: 10.1161/STROKEAHA.112.661587

[132] Prendecki M, Florczak-Wyspianska J, Kowalska M, Lianeri M, Kozubski W, Dorszewska J. Normal aging and dementia. Davide M, editor. In: Update on Dementia. InTech, Rijeka; 2016; 251-272. DOI: 10.5772/64203

[133] Selkoe DJ. Alzheimer's disease: Genes, proteins, and therapy. Physiological Reviews. 2001;**81**:741-766

[134] Alonso Vilatela ME, López-López M, Yescas-Gómez P. Genetics of Alzheimer's disease. Archives of Medical Research. 2012;**43**:622-631. DOI: 10.1016/j.arcmed.2012.10.017

[135] Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nature Genetics. 2013. **45**:1452-1458. DOI: 10.1038/ng.2802

[136] http://www.alzgene.org/- date of access 02.03.2017

[137] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers and Dementia. 2011;**7**:263-269. DOI: 10.1016/j.jalz.2011.03.005

[138] Martin E, Boucher C, Fontaine B, Delarasse C. Distinct inflammatory phenotypes of microglia and monocyte-derived macrophages in Alzheimer's disease models: Effects of aging and amyloid pathology. Aging Cell. 2017;**16**:27-38. DOI: 10.1111/acel.12522

[139] Zhang ZG, Li Y, Ng CT, Song YQ. Inflammation in Alzheimer's disease and molecular genetics: Recent update. Archivum Immunologiae et Therapiae Experimentalis. 2015;**63**:333-344. DOI: 10.1007/s00005-015-0351-0

[140] Parsons CG, Danysz W, Dekundy A, Pulte I. Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer's disease. Neurotoxicity Research. 2013;**24**:358-369. DOI: 10.1007/s12640-013-9398-z

[141] Mendiola-Precoma J, Berumen LC, Padilla K, Garcia-Alcocer G. Therapies for prevention and treatment of Alzheimer's disease. Biomed Research International. 2016;**2016**:2589276. DOI: 10.1155/2016/2589276

[142] Dolejší E, Liraz O, Rudajev V, Zimčík P, Doležal V, Michaelson DM. Apolipoprotein E4 reduces evoked hippocampal acetylcholine release in adult mice. Journal of Neurochemistry. 2016;**136**:503-509. DOI: 10.1111/jnc.13417

[143] Reeve A, Simcox E, Turnbull D. Ageing and Parkinson's disease: Why is advancing age the biggest risk factor? Ageing Research Reviews. 2014;**14**:19-30. DOI: 10.1016/j.arr.2014.01.004

[144] Tata A, Velluto L, D'Angelo C, Reale M. Cholinergic system dysfunction and neurodegenerative diseases: Cause or effect? CNS and Neurological Disorders Drug Targets. 2014;**13**:1294-1303. DOI: 10.2174/18715273136661409171211 32

[145] Troesch B, Weber P, Mohajeri MH. Potential links between impaired one-carbon metabolism due to polymorphisms, inadequate B-vitamin status, and the development of Alzheimer's disease. Nutrients. 2016;**8**:E803. DOI: 10.3390/nu8120803

[146] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. Journal of Neurology, Neurosurgery and Psychiatry. 1992;**55**:181-184. DOI: 10.1136/jnnp.55.3.181

[147] Dorszewska J, Kozubski W. Introductory chapter—genetic and biochemical factors in Parkinson's disease. Dorszewska J, Kozubski W, editors. In: Challenges in Parkinson's disease. InTech, Rijeka; 2016; 1-6. DOI: 10.5772/61880

[148] Przedborski S, Jackson-Lewis V. Mechanisms of MPTP toxicity. Movement Disorders. 1998;**13**:35-38

[149] Nagatsu T, Mogi M, Ichinose H, Togari A. Changes in cytokines and neurotrophins in Parkinson's disease. Journal of Neural Transmission. 2000;**60**(Supplementum): 277-290

[150] Bartels AL, Leenders KL. Cyclooxygenase and neuroinflammation in Parkinson's disease neurodegeneration. Current Neuropharmacology. 2010;**8**:62-68. DOI: 10.2174/157015910790909485

[151] Litteljohn D, Mangano E, Clarke M, Bobyn J, Moloney K, Hayley S. Inflammatory mechanisms of neurodegeneration in toxin-based models of Parkinson's disease. Parkinson's Disease. 2011;**2010**:713517. DOI:10.4061/2011/713517

[152] Goldman SM. Environmental toxins and Parkinson's disease. Annual Review of Pharmacology and Toxicology. 2014;**54**:141-164. DOI: 10.1146/annurev-pharmtox-011613-135937

[153] Golts N, Snyder H, Frasier M, Theisler C, Choi P, Wolozin B. Magnesium inhibits spontaneous and iron-induced aggregation of alpha-synuclein. Journal of Biological Chemistry. 2002;**277**:16116-16123. DOI: 10.1074/jbc.M107866200

[154] Bartzokis G, Tishler TA, Shin IS, Lu PH, Cummings JL. Brain ferritin iron as a risk factor for age at onset in neurodegenerative diseases. Annals of the New York Academy of Sciences. 2004;**1012**:224-236. DOI: 10.1196/annals.1306.019

[155] Oczkowska A, Kozubski W, Lianeri M, Dorszewska J. Genetic variants in diseases of the extrapyramidal system. Current Genomics. 2014;**15**:18-27. DOI: 10.2174/1389202914666131210213327

[156] Dorszewska J, Kowalska M, Blaszczak W, Kozubski W. Molecular basis of neurodegeneration in Parkinson's disease. In: Neurodegenerative Diseases: Overview, Perspectives and Emerging Treatment. NY, USA: NOVA Sciences Publishers, Inc; 2017. [in press].

[157] Raver SM, & Lin S-C. Basal forebrain motivational salience signal enhances cortical processing and decision speed. Frontiers of Behavioral Neuroscience. 2015;**9**:eCollection 2015. DOI: 10.3389/fnbeh.2015.00277

[158] Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proceedings of the National Academy of Sciences. 1987;**84**:5976-5980

[159] Buchman AS, Shulman JM, Nag S, Leurgans SE, Arnold SE, Morris MC, Schneider JA, Bennett DA. Nigral pathology and parkinsonian signs in elders without Parkinson disease. Annals of Neurology. 2012;**71**:258-266. DOI: 10.1002/ana.22588

[160] Horvath S, Ritz BR. Increased epigenetic age and granulocyte counts in the blood of Parkinson's disease patients. Aging (Albany NY). 2015;**7**:1130-1142. DOI: 10.18632/aging.100859

[161] Matsumoto L, Takuma H, Tamaoka A, Kurisaki H, Date H, Tsuji S, Iwata A. CpG demethylation enhances alpha-synuclein expression and affects the pathogenesis of Parkinson's disease. PLoS One. 2010;**5**:e15522. DOI: 10.1371/journal.pone.0015522

[162] Goers J, Manning-Bog AB, McCormack AL, Millett IS, Doniach S, Di Monte DA, Uversky VN, Fink AL. Nuclear localization of alpha-synuclein and its interaction with histones. Biochemistry. 2003;**42**:8465-8471. DOI: 10.1021/bi0341152

[163] Elahy M, Jackaman C, Mamo JC, Lam V, Dhaliwal SS, Giles C, Nelson D, Takechi R. Blood–brain barrier dysfunction developed during normal aging is associated with inflammation and loss of tight junctions but not with leukocyte recruitment. Immunity and Ageing. 2015;**12**:2. DOI: 10.1186/s12979-015-0029-9

[164] Cabezas R, Avila M, Gonzalez J, El-Bachá RS, Báez E, García-Segura LM, Jurado Coronel JC, Capani F, Cardona-Gomez GP, Barreto GE. Astrocytic modulation of blood brain barrier: Perspectives on Parkinson's disease. Frontiers in Cellular Neuroscience. 2014;**8**:211. DOI: 10.3389/fncel.2014.00211

[165] Białecka M, Kurzawski M, Roszmann A, Robowski P, Sitek EJ, Honczarenko K, Gorzkowska A, Budrewicz S, Mak M, Jarosz M, Gołąb-Janowska M, Koziorowska-Gawron E, Droździk M, Sławek J. Association of COMT, MTHFR, and SLC19A1(RFC-1) polymorphisms with homocysteine blood levels and cognitive impairment in Parkinson's disease. Pharmacogenetics Genomics. 2012;**22**:716-724. DOI: 10.1097/FPC.0b013e32835693f7

[166] Białecka M, Robowski P, Honczarenko K, Roszmann A, Sławek J. Genetic and environmental factors for hyperhomocysteinaemia and its clinical implications in Parkinson's disease. Polish Neurology and Neurosurgery. 2009;**43**:272-285. In Polish

[167] Zoccolella S, Lamberti P, Armenise E, de Mari M, Lamberti SV, Mastronardi R, Fraddosio A, Iliceto G, Livrea P. Plasma homocysteine levels in Parkinson's disease: Role of antiparkinsonian medications. Parkinsonism and Related Disorders. 2005;**11**:131-133. DOI: 10.1016/j.parkreldis.2004.07.008

[168] Mattson MP, Shea TB. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends in Neurosciences. 2003;**26**:137-146. DOI: 10.1016/S0166-2236(03)00032-8

[169] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of tumors of the central nervous system: A summary. Acta Neuropathologica. 2016;**131**:803-820. DOI: 10.1007/s00401-016-1545-1

[170] Lorimer CF, Saran F, Chalmers AJ, Brock J. Glioblastoma in the elderly — How do we choose who to treat?. Journal of Geriatric Oncology. 2016;**7**:453-456. DOI: 10.1016/j.jgo.2016.07.005

[171] Mohile NA. How I treat glioblastoma in older patients. Journal of Geriatric Oncology. 2016;**7**:1-6. DOI: 10.1016/j.jgo.2015.12.001

[172] Schneider T, Mawrin C, Scherlach C, Skalej M, Firsching R. Gliomas in adults. Deutsches Arzteblat International. 2010;**107**:799-807. quiz 808. DOI: 10.3238/arztebl.2010.0799

[173] Scott JG, Bauchet L, Fraum TJ, Nayak L, Cooper AR, Chao ST, Suh JH, Vogelbaum MA, Peereboom DM, Zouaoui S, Mathieu-Daude H, Fabbro-Peray P, Rigau V, Tailandier L, Abrey LE, DeAngelis LM, Shih JH, Iwamoto FM. Recursive partitioning analysis of prognostic factors for glioblastoma patients aged 70 years or older. Cancer. 2012;**118**:5595-5600. DOI: 10.1002/cncr.27570

[174] Rampling R, Erridge S. Management of Central Nervous System Tumours in the elderly. Clinical Oncology (Royal College of Radiologists (Great Britain)). 2014;**26**:431-437. DOI: 10.1016/j.clon.2014.03.009

[175] Schittenhelm J, Skardelly M. Molecular advances In Glioblastoma Neuropathology. Agrawa A, editor. In: Neurooncology–Newer Developments. InTech, Rijeka; 2016; 3-26 DOI: 10.5772/62670

[176] Ahmed R, Oborski MJ, Hwang M, Lieberman FS, Mountz JM. Malignant gliomas: Current perspectives in diagnosis, treatment, and early response assessment using advanced quantitative imaging methods. Cancer Management and Research. 2014;**6**:149-170. DOI: 10.2147/CMAR.S54726

[177] Verhaak RGW, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, Alexe G, Lawrence M, O'Kelly M, Tamayo P, Weir BA, Gabriel S, Winckler W, Gupta S, Jakkula L, Feiler HS, Hodgson JG, James CD, Sarkaria JN, Brennan C, Kahn A, Spellman PT, Wilson RK, Speed TP, Gray JW, Meyerson M, Perou CM, Hayes DN, Cancer Genome Atlas Research Network, The Cancer Genome Atlas Research, Cancer Genome Atlas Research Network TCGAR. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010, **17**:98-110. DOI: 10.1016/j.ccr.2009.12.020

[178] Flowers A. Brain tumors in the older person. Cancer Control: Journal of the Moffitt Cancer Center. 2000;**7**:523-538

[179] Jordan JT, Gerstner ER, Batchelor TT, Cahill DP, Plotkin SR. Glioblastoma care in the elderly. Cancer. 2016;**122**:189-197. DOI: 10.1002/cncr.29742

[180] Kita D, Ciernik IF, Vaccarella S, Franceschi S, Kleihues P, Lütolf UM, Ohgaki H. Age as a predictive factor in glioblastomas: Population-based study. Neuroepidemiology. 2009;**33**:17-22. DOI: 10.1159/000210017

[181] Narita Y. Bevacizumab for glioblastoma. Therapeutics and Clinical Risk Management. 2015;**11**:1759-1765. DOI: 10.2147/TCRM.S58289

[182] Cohen AL, Colman H. Glioma biology and molecular markers. Cancer Treatment and Research. 2015;**163**:15-30. DOI: 10.1007/978-3-319-12048-5_2

[183] Wirsching H-G, Galanis E, Weller M. Glioblastoma. Handbook of Clinical Neurology. 2016;**134**:381-397. DOI: 10.1016/B978-0-12-802997-8.00023-2

[184] Specenier P. Bevacizumab in glioblastoma multiforme. Expert Review on Anticancer Therapy. 2012;**12**:9-18. DOI: 10.1586/era.11.179

[185] Nghiemphu PL, Liu W, Lee Y, Than T, Graham C, Lai A, Green RM, Pope WB, Liau LM, Mischein PS, Nelson SF, Elashoff R, Cloughesy TF. Bevacizumab and chemotherapy for recurrent glioblastoma: A single-institution experience. Neurology. 2009;**72**:1217-1222. DOI: 10.1212/01.wnl.0000345668.03039.90

[186] Ohgaki H. Genetic pathways to glioblastomas. Neuropathology. 2005;**25**:1-7. DOI: 10.1111/j.1440-1789.2004.00600.x