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Alzheimer's disease - etiology and pathogenesis

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Abstract

Alzheimer's disease (AD) is one of the neurodegenerative diseases of the senile age that is most prevalent in the modern world. With regard to the population of people aged 60 years, the incidence of Alzheimer's disease is estimated at 1%, while in the population of people aged 90 and over even up to 50%. This type of dementia causes serious deficits in cognitive functions. From the neuroanatomical

point of view, the changes taking place in the brain are the result of the disappearance of areas within the hippocampus, additionally, as one of the key causes of this disease, the accumulation of beta-amyloid in brain tissue is considered. The consequence of many changes is the loss of neurons, aggregation of amyloid plaques and the formation of tau protein into tangles.

There are many hypotheses regarding the mechanisms and causes of the AD, but there are still many doubts about the existing health problem of older people. The aim of the study is to investigate the etiology and pathogenesis of AD in the context of the current state of knowledge and possible prognoses for the future in the light of research into this disease.

Keywords: dementia, Alzheimer's disease, etiology, pathogenesis

1. Introduction

Long-term observations related to the phenomenon of an aging society, lead to the continuous need to monitor the processes related to this. In Poland, at the end of 2014, people over 60 were 8.5 million, over 22% of the total population, while taking into account the forecast of the Central Statistical Office of Poland in 2050, people over 60 are to be over 40% [1]. In connection with the above, the problem of proper diagnostics and therapy of diseases of the old age is of great importance. Alzheimer's disease (AD), which is an example of "senile dementia", is the most common cause of dementia. With regard to the population of people aged 60, the incidence of Alzheimer's disease is estimated at 1%, whereas in the population of people aged 90 and over even up to 50% [2].

2. Purpose of work

The aim of the study is to investigate the etiology and pathogenesis of AD in the context of the current state of knowledge and possible prognoses for the future in the light of research into this disease.

3. Description of knowledge

In general terms, this disease is caused by the loss of many types of nerve cells in the cerebral cortex, and the process may start around the age of 35, while significant symptoms occur most often when the loss of neurons reaches values ranging from 60% to 75% decay of cerebral nerve cells, which is no longer able to compensate for deficiencies and thus exceeds the threshold of cognitive mechanisms [3, 4]. Neurochemical causes of Alzheimer's disease concern the death of nerve cells due to the formation of abnormal protein aggregates that form filamentous structures - neurofibrillary tangles (NFTs) that fill neurons and senile plaques,

located outside neurons. The cause of dementia appearing in Alzheimer's disease is in the first stage damage to cholinergic neurons, the earliest atypical proteins appear in the glutamatergic neurons of the entorhinal cortex, and then the hippocampus and associative cortex, ie in the structures responsible for memory and perception. As a result of the development of the disease, glutamatergic, cholinergic, later serotonin and noradrenergic neurons are eradicated, while the most resistant ones are gabaergic neurons. One of the most important causes of cognitive impairment, a key symptom of Alzheimer's disease, is the failure of signalling in the forebrain cholinergic system, caused by the loss of cholinergic neurons. The aforementioned system is responsible for the processes of attention and recall of previously stored memory traces [5, 6, 7].

It is worth paying attention to other heavily damaged neurons using, as a signal of noradrenaline and serotonin, the effects of these lesions can be conditioned by psychiatric disorders and behavioral disorders such as [8]: delusions, verbal aggression, physical aggression, screaming, obscenity, vulgarity, etc. Neurodegenerative changes primarily affect the cerebral cortex and hippocampus, as well as the amygdala, forebrain cholinergic system and brainstem nuclei. In terms of memory disorders, this is related to damage to the hippocampus and medial temporal cortex. Neuropathological changes in the case of the new cortex determine cognitive dysfunction, anxiety disorders, mainly dependent on the amygdala, while damage to the forebrain cholinergic system results in the appearance of attention deficits and learning [9,10,11] (Figure 1).

Alzheimer's disease appears spontaneously, although the genetic basis of the familial form of the disease (familiar Alzheimer's disease - FAD) is also known, they are conditioned by autosomal mutations dominating in 3 genes: APP (amyloid precursor protein), presenilin 1 (PS1) and presenilin 2 (PS2). In the primary histopathological picture, extracellular senile plaques consisting of β-amyloid (Aβ) and intracellular neurofibrillary tangles (NFT) [12, 13, 14, 15] are ligated.

An important issue in the pathogenesis of Alzheimer's disease is the incorrect structure and function of the tau protein responsible for the stabilization of microtubules in neurons. In this case, hyperphosphorylation and polymerization of the tau protein occurs, followed by loss of its affinity for microtubules, which in turn leads to destabilization of the cytoskeleton [12, 13].

Hyperphosphorylated tau protein (MAPT) has a tendency to aggregate and create neurofibrillary tangles (NFT), areas of the brain in which the abnormal structure and function of tau protein are significantly observed, associate cortex, entorhoid cortex, hippocampus, parotocampal bend and the amygdala [15].

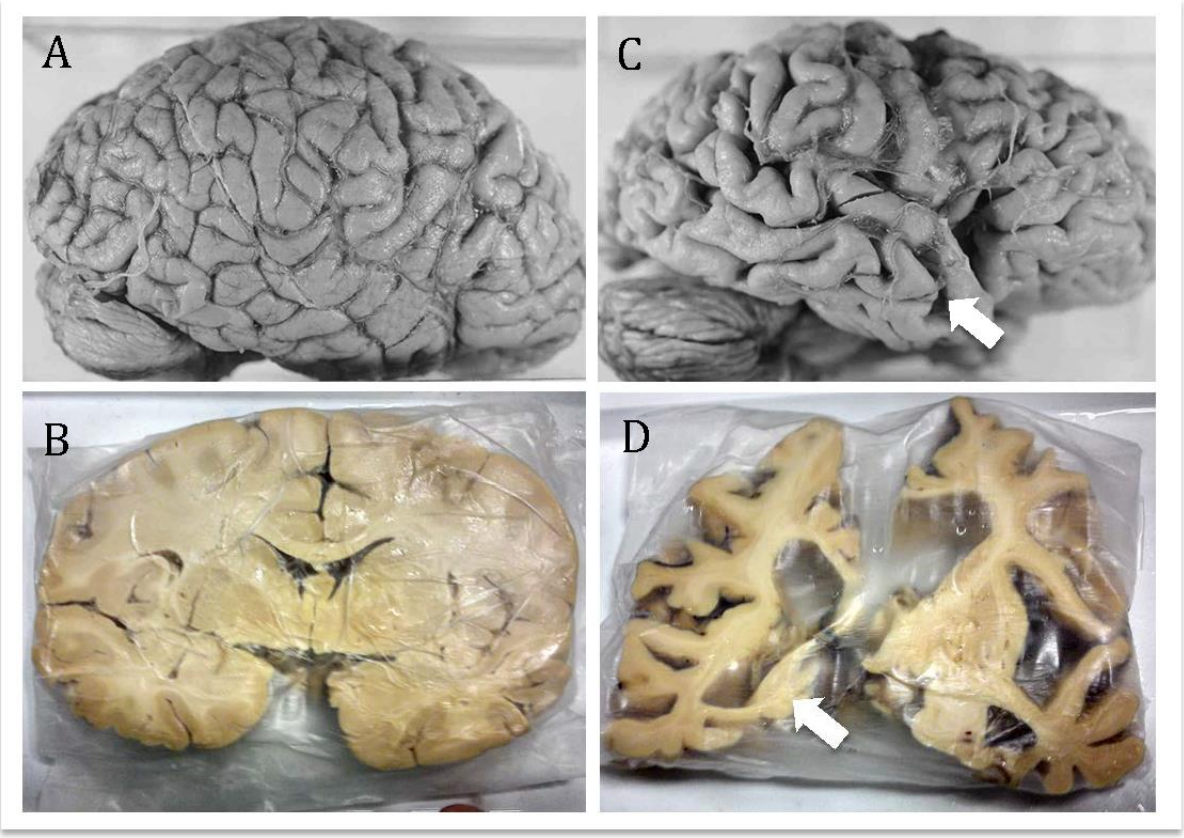

Figure 1. Post-mortem comparison of normal brain and Alzheimer's disease. A, B) Normal brain. C, D) The brain with AD pathology. B) Atrophy in the fronto-temporal areas, ventricular enlargement and selective disappearance of the hippocampus (arrows) [16].

The pathogenesis process of Alzheimer's disease in the initial phase concerns abnormal amyloid precursor β (APP) transformation, involving β- and γ-secretase, and its fragmentation into insoluble β-amyloid forms, which is first accumulated intracellularly and then extracellularly. in the form of senile plaques. The appearance of insoluble forms of β-amyloid determines the hyperphosphorylation of the tau protein, which binds to microtubules, thanks to which it enables them to stabilize. Under normal conditions, the tau protein is present in the brain in the form of 6 isoforms and is associated with the MAPT gene (17q21) (MAPT). In the case of the MAPT mutation, tau proteins will be readily phosphorylated and their affinity for microtubules will occur. As a consequence, the occurrence of improper construction and change in the functionality of the tau protein leads to disturbances in intraxonal transport, while the tau protein (hyperphosphorylated) is accumulated in the form referred to as neurofibrillary degeneration leading to neuronal death. In reference to β-amyloid, it should also be mentioned about its accumulation in the walls of small cerebral vessels in the cortical layer, this may result in the appearance of outbreaks of microcortures located in the cortical structures [17]. Neurodegenerative changes lead to neuronal death and the loss of inter-neuronal connections. They result in a decrease in the level of relay substances, of which

the reduction in the acetylcholine content is the most important for the memory system, while the determination of the number and distribution of senile plaques and neurons with the features of neurofibrillary degeneration is the basis for the neuropathological classification of Alzheimer's disease [17].

Studies using animal models of Alzheimer's disease have made great progress in understanding the pathogenesis of this disease. Currently, the most popular models are mouse models, due to their low price, relatively short lifespan and the possibility of observing typical symptoms of Alzheimer's disease, as well as high potential for genetic modification in these organisms [14,15].

With regard to the use of other animals as a model of Alzheimer's disease, the use of transgenic technologies has some limitations, although rat models of this disease are known, and even invertebrates [18,19,20].

The usefulness of transgenic organisms, as a model of Alzheimer's disease, is determined by specific criteria, eg pathological changes should be genetically conditioned, in addition, the transgenic organism should be able to express the phenotypic features of the human disease, physiological and behavioral [10,14].

The use of transgenic mice as a model of Alzheimer's disease enables accurate examination of disease progression and their role in research on new therapies is equally important. The identification of genes that are responsible for the direct connection with the development of the disease has allowed the animal models to be modeled with various mutations and then the correlation between a particular genetic defect and its phenotypic symptom on different levels (biochemical, morphological, anatomical, behavioral) [10, 14, 15, 21].

Transgenic mice (PDAPPs) are the most popular model created today, thanks to the use of the platelet promoter, which activates the human minigin APP, conditioning the occurrence of a point mutation, which consists in replacing one valine residue with the phenylalanine residue. In humans, this mutation causes a rare family form of Alzheimer's disease characterized by an early onset of symptoms, in the mouse model as a result of strong expression of APP and amyloid deposition, senile plaques are observed, cognitive disorders appear quite quickly (usually deterioration in learning). This model is very interesting, because there is a deposition of β-amyloid in a similar way to that which can be observed in the course of the disease in the human brain, although this model does not show other characteristic features of Alzheimer's disease, i.e. the formation of neurofibrillary tangles and mass neuronal death [22,23,24,25]

Contemporary knowledge about the mechanisms leading to neurodegenerative changes, however, is not complete, and Alzheimer's disease due to the lack of effective treatment

remains an incurable and fatal disease [26].

4. Conclusions

Today, much attention in the world and Polish literature is devoted to the study of mechanisms of pathogenesis of many neurodegenerative diseases (especially Alzheimer's) and finding suitable animal models of these diseases, thus providing the necessary research space for testing and creating new therapeutic options. In the context of the analyzed subject matter and literature referring to this disease, research in this field is fully valid and justified, and what is more, necessary.

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