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Biochemical Basics of Alzheimer's Disease

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Abstract: The biochemical basics of Alzheimer's disease are considered in the article at the level of neurotoxic amyloid level and the prevention measures, which may decrease the risks of Alzheimer's disease.

Keywords:- *Alzheimer's disease, amyloids, enzyme secretase.*

I. INTRODUCTION

Neurodegenerative and neuropsychiatric progressive disorders of the brain were discovered at the beginning of the last century, in a German woman Augusta D. in 1901. In 1906 this disease was described by German psychiatrist Alois Alzheimer and in his honor E. Krepelin called it Alzheimer's disease in 1910.

II. LITERATURE REVIEW

About 25 years ago an opinion was expressed to mark dementia at the earliest age that Alzheimer's disease (AD) was due to insufficiency of central cholinergic system. This was confirmed by: 1) the significant disorders were revealed at the level of cholinergic neurons. The light forms of Alzheimer's disease were revealed in old-aged people; 2) The cognitive function of the patients was noticeably improved under the impact of pharmacological compounds of cholinergic type; 3) Cholinesterase inhibitors have been found to be particularly important for the treatment of Alzheimer's disease. According to the latest investigations, along with acetylcholine the other neurotransmitters also take an active participation in Alzheimer's disease. It should be noted that at present in the USA more than 1 million dollars are spent for the diagnostics, treatment and institutional supervision of Alzheimer's disease. During the last 5 years the number of people suffering from Alzheimer's disease has exceeded 5 million. It is assumed that by 2030 this index will exceed 7 million, and by 2050 – 16 million, accordingly the mortality rate will significantly increase [1-3].

Alzheimer's disease may be determined genetically, or evoked by family and ecological reasons (sporadic). 15% of Alzheimer's disease has a family character (heredodegenerative type) and over the last 5 years has been progressively developed; this is due to a massive death of neurons in frontal, temporal and parietal lobes of the big hemispheres [9, 16, 23]. Two histopathological correlates characteristic of this disease are noted: the so-called senile plaques containing the substances of amorphic amyloid type and the accumulation of thickened fibrillar components condensed as glomerulus in the neurons (Alzheimer's neuro fibrous glomerulus). In some cases the above-said histopathological changes develop in parallel with older age. Alzheimer's disease very often and relatively earlier is formed in the patients with Down syndrome, which indicate the generic defect of the 21 chromosome in the formation of neurodegenerative condition. The family cases are due to the mutation of the 14^{th} chromosome. It has been established that the existence of lipoprotein E_4 (along with allelic gene E_4) enhances the risk of Alzheimer's disease development.

One of the first clinical signs of this disease is memory impairment as a result of the damages to the cortex and hippocampus. Very often the apoptosis is actively involved in the process, an intensive accumulation of amyloids and the surplus of β-peptides (AB) are observed. AB is formed from a precursor protein of large-sized amyloid (APP), the gene of which resides in the 21^{st} chromosome [7, 23]. Two different genes and protein presenelin [6], causing Alzheimer's disease have been separated. The latter must be involved in the transport and decay of APP. The precursor of amyloid APP appears to be an izoform transmembranous protein. As a result of its decay, the insoluble forms are obtained, while under the action of α-secretase a soluble fragment sAPPα is received. AB is partially presented in it. The separation of AB from APP takes place by means of β–and α- secretase [24]. The negative impact of AB on the brain mainly is due to their neurotoxic nature. One of the causing reasons of Alzheimer's disease is considered to be EY gene, coding apolipoprotein (apo-EY), which resides in the 19th chromosome. Its predominant risk-factor is APO-E4. By the impact of the latter the transport of cholesterol, causing atherosclerosis, though the correlation between the activity of APO-E4 and psychonervous disorders has not been revealed [5, 13, 26, 29].

There is other opinion, according to which Alzheimer's disease may be induced by the viruses, the surplus of aluminum ions, a low level of choline acetyltransferase synthesizing acetylcholine [21. AD is related with inflammatory processes, which is confirmed by the involvement of cytokine TNF-α in the inflammatory processes. As compared to other cytokines, TNF-α more strongly activates microglial cells, connected to the nervous axon nodes and the secretion of TNF-α from microglia. The latter promotes the creation of free radicals and oxidative damage to nervous cells [20]. Finally, in conditions of AD, the neuronal cells die as a result of apoptosis enhancement [19]. At the first stage, by means of IL-1 the synthesis of amyloids and TNF-α from the precursor protein APP is activated. In

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parallel, IL-1 and TNF-α activate the synthesis of α1-antichymotrypsin (AC-T), which is critical in the origin of β–amyloid fibrils. Under the impact of the induction of free radicals and the synthesis of toxic glutamate also enhance, and as a result, the self-destruction of cells by apoptosis is observed under the action of β–amyloid, TNF- α, toxic glutamate and free radicals [10, 19].

Although neuropathological studies showed that early-onset Alzheimer's disease (EAD) and mild dementia were indistinguishable, the clinical studies suggested that EAD and late-onset Alzheimer's disease (LAD) were cognitively distinct. The EAD and LAD groups did not differ according to dementia or the most cognitive variables. As compared to EAD, the LAD group had worse functional responsibilities and motor-executive functions. These differences disappeared, when age differences were taken into account. We conclude that Alzheimer's disease is a clinically heterogeneous disorder, the manifestations of which can vary with age onset. These differences indicate the age-related vulnerabilities in this disease [14]. Attention has attracted the fact that at Alzheimer's disease, the memory impairment is controlled by ApoE (apo-protein E) gene, by the action of which the biosynthesis of that protein is regulated that conditions homeostasis of lipids in the brain. At AD, Apo 2, Apo 3 and Apo 4 were especially strong risk-factors of dementia and amentia, which condition the accumulation of β–amyloids in the brain and the activation of Alzheimer's disease.

At Alzheimer's disease, the pre- and postsynaptic proteins of the neuron were specially studied: 3 vesicular proteins (synaptotagmin, synaptophysin, Rab 3A), 2 proteins of synaptic membrane (Gap 43, synaptobrevin), and 2 postsynaptic proteins (neurogranin, synaptopodine). At AD, the above-mentioned proteins significantly decreased in older people, as compared to healthy people, which especially clearly were revealed in the frontal cortex. It has been established that synaptic protein p35 in the associated condition with syntaxin I and p58 specifically interacts with pre-synaptic channels and SNARE proteins, and actively participates in calcium dependent neurotransmitters in exocytosis. As it has been revealed, all this is related to synapse pathogenesis at a level of synapse vesicles. As compared to the control, at early onset of Alzheimer's disease (EAD), the content of proteins in the synaptic vesicles of frontal cortex reduces by 30-70%, while at late onset of Alzheimer's disease (LAD) – by 82-88% and in the hippocampus – by 22-82%.

Genetic disorders appear to be the highest genetic factor of Alzheimer's disease. It has been established that if genetic disorders appear to be the reason for this disease in 80% of 12.000 pairs of twins, and if one of the twins is diagnosed with Alzheimer's disease, then in 55% of cases his/her partner sooner or later will be diagnosed with this disease. A lot of pharmaceutical companies are interested to create a medication for the treatment of Alzheimer's disease, though, despite some achievements, there are no serious successes up today. Recently information on the use of green tea for the treatment of Alzheimer's disease has been reported. There is an opinion that medicinal properties of green tea are due to an excess amount of polyphenols, as antioxidants, in tea leaves. In 2005 an interesting article was published about the retention of Alzheimer's disease development by the action of β-secretase (BACEI). It has been shown that by the action of β-secretase, as a result of the decay of amyloid precursor protein the insoluble proteins are accumulated in the brain and amyloid plaques are created. Proceeding from the above-mentioned, the authors considered perspective to retain the action of BACEI for the treatment of AD. For this aim a modified small interfering RNA - an inhibitor of BACEI coding genes - was administered into the brain by lentivirus. It has been shown that during one month after the treatment with lentivirus, the mice with memory loss practically recover the ability to solve a labyrinth task and the memory improves. In parallel, a new neurophysiological technology was developed for early diagnostics of Alzheimer's disease. It has been shown that out of 60 completely healthy people only 6 have dementia, who before the Alzheimer's disease during magnetic resonance scans of the brain show a low physiological activity in temporal and parietal lobes.

It has been shown that β-amyloid peptide has a central role in the pathogenesis of Alzheimer's disease. Amyloid plaques which are mainly composed of β-amyloid peptide, gradually rouse in the brain of AD patients. The therapeutic strategies included reducing β- amyloid levels by inhibiting the enzymes, called β- and □-secretase (BACE1, BACE2). The latter inhibits the generation of amyloids from APP. BACE1 and BACE2 appear to be the important enzymes for the protection of patients with AD [4]. The retention of Alzheimer's disease development is possible by the inhibition of enzyme β- secretase (BACEI), under the action of which the creation of insoluble β-neurotoxic amyloid plaques takes place in the brain. Based on the above, the use of β-secretase inhibitor for the treatment of Alzheimer's disease is considered to be promising. The experiments continue in this direction [25]. Based on the other methodological approaches, the changes in the sizes of brain structural formations attract attention in the people, suffering from Alzheimer's disease. In particular, it has been noted that the hippocampus size significantly decreases in the people suffering from Alzheimer's disease. Based on the above-said, it becomes possible to assume the expected disease preliminary and to carry out preventive measures, according to the sizes of brain structures [27]. According to the newest data, an inhibitory vaccine against Alzheimer's disease has already been created in Japan [12, 15, 22]. Professor of Kyoto University in Japan J. Nishimoto discovered protein gumanin, which inhibits the development of Alzheimer's disease [17]. The results of immunotherapy researches for the treatment of Alzheimer's disease have caused a special interest [28]. According to the authors, the results of preliminary studies seem to be very promising for the treatment of Alzheimer's disease. The

vaccine was tested on the genetically modified mice that were prone to Alzheimer's disease. The test has a great success. A virus that carries the β amyloid synthesizing gene was involved in the vaccine. The idea of creating this vaccine was to strengthen the immune system with it, which would be directed to get the information on harmful proteins, causing Alzheimer's disease and to destroy them.

As has been shown under the influence of this vaccine the accumulations of amyloid protein significantly decrease in the brain. The full normalization of learning ability of a rat took place after 3 months of treatment. Unfortunately, now it is difficult to make a serious conclusion, as several years ago in England during the treatment with this vaccine several patients participating in the experiment died with encephalomyelitis. Dr. Randall Bateman – a researcher from the Washington University in St. Louis made a blood test public that could reveal Alzheimer's disease before a patient manifested physical symptoms. After this, Japanese and Australian team of scientists published a study on a blood test that could detect Alzheimer's disease with 90% accuracy [12, 15]. At Alzheimer's disease, when the memory is destroyed, a nerve growth factor is often administered into the brain for the treatment of patients [18], and as a result, the memory and information reproduction significantly improve. Alzheimer's disease is rarely found in the population of Nigeria. Naturally, the scientists got interested in this fact. As it turned out, in Nigeria the food vegetables are rich of anticholinesterase substances, which inhibit the activity of enzyme acetylcholinesterase and at the expense of the accumulation of acetylcholine - the excitatory neurotransmitter - the neurons and neuronal ensembles remain in an active condition.

Out of the 22 plants spread in Nigeria, the extract of root crust of *Spondias mombin* inhibits acetylcholinestarase by 83.94%, *Callophinophyllum inophyllum* – by 58.52%, the leaves of *C. jagus* – by 74.25%, the leaves of stem bark of *Combretum molle* – by 90.42 and 88.13%, respectively. Based on it, the scientists conclude that to take the above-said plants as food or as ingredients should be considered as one of the prerequisites for the prevention of Alzheimer's disease [8]. By means of tomography it has been established that the structural disorders are especially sharply expressed in the brain specific areas of people suffering from Alzheimer's disease, as compared to healthy ones. Recently the researchers have focused on the levels of nicotineamidemononucleotide adenylyl transferase 2 (NMNAT2), which is known to produce adenine dinucleotide (NAD). The latter protects the brain from oxidative stress, triggered by the excess of nerve cell activity. Based on their analysis, the researchers found that adults, who had NMNAT2 higher levels in the brain, were less likely to have experienced cognitive decline; the individuals with lower levels of this enzyme were more likely to have had dementia [11]. It's true that today there is no real possibility for the treatment of Alzheimer, but the specialist of psycho- and music therapy express their opinion that reading books, playing chess, solving crosswords and puzzles, learning foreign languages, playing musical instruments, and other activities significantly enhance the activity of neurons and neuronal ensembles. It is impossible to leave the nervous system in the hypokinetic state for a long time, because the neurons and neuronal ensembles, deprived of biological signals, lose the synapses and die [3, 4]. Taking vegetables and fruit, rich in vitamins is also useful for the brain neurons [2]. Be optimistic, avoid aggressive social environment and isolated life. The stress appears to be one of the risk-factors, activating Alzheimer's disease. It should be noted that joyful life is better, than medications.

Recently medicine workers offer us the medication piribedil, activating dopaminergic, and noradrenergic systems in the treatment of people suffering from Alzheimer's disease. Under its action the memory and the concentration of the attention to the perceived material significantly improve. For the improvement of blood circulation in the brain the medications – pentoxifyline and vinpocetine – the inhibitors of phosphodiesterase are also used, by means of which a vascular expansion takes place and blood rheological properties improve. The blockers of calcium channels are also widely used. A standard extract of Ginkgo biloba, α-adrenoblocker nicergoline, peptidergic amino acids, etc. are proposed for the treatment of moderate dementia, however, still there are no real therapeutic drugs. Using the proposed preparations only a partial improvement of dementia is possible. Probably, the patients themselves should also act, avoid external stimuli, strengthen their social activities and prevent a long-term stay of neurons and nerve ensembles in the hypokinetic state.

III. CONCLUSION

The reasons of Alzheimer's disease and the issues of its treatment and prevention by the use of modern technologies are considered in this article.

REFERENCES

[1]. Berchtold N.C., Cotman C.W. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. Neurobiol. Aging, 1998; 19 (3):173–189.
[2]. Boothby L.A., Doering P.L. Vitamin C and vitamin E for Alzheimer's disease. Ann. Pharmacother., 2005; 39 (12):2073–80.
[3]. Brookmeyer R., Gray S., Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am. J. Public Health, 1998; 88 (9): 1337–1342.
[4]. Butz M., Wörgötter F., van Ooyen A. Activity-dependent structural plasticity. Brain Res. Rev., 2009; 60:287–305.
[5]. Butz M., Ooyen A. A. Simple Rule for Dendritic Spine and Axonal Bouton Formation Can Account for Cortical Reorganization after Focal Retinal Lesions. Published: October 10, 2013;

http://dx.doi.org/10.1371/journal.pcbi.1003259.
[6]. Cai D., Netzer W.J., Zhong M. et al. Presenilin-1 uses phospholipase D1 as a negative regulator of beta-amyloid formation. Proc. Natl. Acad. Sci., U.S.A. 2006; 103 (6):1941– 1946.
[7]. Défossez A., Delacourte A. Transformation of degenerating neurofibrils into amyloid substance in Alzheimer's disease: histochemical and immunohistochemical studies. J. Neurol. Sci., 1987; 81(1):1-10.
[8]. Elufioye T.O., Obuotor E.M., Sennuga A.T., Gbedahunsi J.M., Adesanya S.A. Acetylcholinesterase and butyrylcholinesterase inhibitory activity of some selected Nigerian medicinal plants. Rev. bras. farmacogn. 2010; 20(4):472477.
[9]. Ennett D.A., Schneider J.A., Tang Y., Arnold S.E., Wilson R.S. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. Lancet Neurol., 2006, 5 (5): 406–412.
[10]. Gray S.L., Anderson M.L., Crane P.K., Breitner J.C., McCormick W., Bowen J.D., Teri L., Larson E. Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. J. Am. Geriatr. Soc., 2008, 56 (2): 291–295. http://www.lacrescentachiropractor.com/index.php?p=238954
[11]. Honor Whiteman. Brain enzyme could prevent Alzheimer's, neurodegenerative disease, 2016; https://www.medicalnewstoday.com/articles/310696.php 20.
[12]. Hopes rise again for Alzheimer's drug after study by Biogen and Japan's Eisai. NATIONAL / SCIENCE & HEALTHFUL 28, 2018; HTTPS://WWW.JAPANTIMES.CO.JP/TAG/ALZHEIMERS- DISEASE
[13]. Kim J., Basak J.M., and Holtzman D.M. The Role of Apolipoprotein E in Alzheimer's Disease. Neuron, 2009; 63(3):287–303.
[14]. Licht E.A., McMurtray A.M., Saul R.E., Mendez M.F. Cognitive differences between early- and late-onset Alzheimer's disease. Am. J. Alzheimer's Dis. Other Demen., 2007; 22(3):218- 222.
[15]. Morgan R.R. @ Morgan R.A. Published 10:00 AM at Mon, 5 March 2018; Updated 10:25 AM ET Mon, 5 March 2018.
[16]. Mölsä P.K., Marttila R.J., Rinne U.K. Survival and cause of death in Alzheimer's disease and multi-infarct dementia. Acta Neurol. Scand., 1986; 74 (2): 103–107.
[17]. Nishimoto J. Japan scientists find possible Alzheimer's cure. May 22, 2001; Posted: 10:20 AM EDT (1420 GMT).
[18]. Nordberg A. Pharmacological treatment of cognitive dysfunction in dementia disorders. First published: December 1996; https://doi.org/10.1111/j.1600-0404.1996.tb00379.x
[19]. Nunomura A., Chiba S. Avoidance of Apoptosis in Alzheimer's Disease. J. Alzheimer's Dis., 2000; 2(1):59-60.
[20]. Pfeffer K. Biological functions of tumor necrosis factor cytokines and their receptors. Cytokine Growth Factor Rev., 2003; 14(3-4):185-91.
[21]. Rondeau V. A review of epidemiologic studies on aluminum and silica in relation to Alzheimer's disease and associated disorders. Rev. Environ. Health, 2002; 17 (2): 107–21.
[22]. Scientists look to Chinese soup ingredients to treat dementia. SIA PACIFIC / SCIENCE & HEALTH, SEP. 27, 2018; HTTPS://WWW.JAPANTIMES.CO.JP/TAG/ALZHEIMERS- DISEASE/ .
[23]. Tiraboschi P., Hansen L.A., Thal L.J., Corey-Bloom J. The importance of neuritic plaques and tangles to the development and evolution of AD. Neurology, 2004; 62 (11): 1984–9.
[24]. Tyler S.J., Dawbarn D., Wilcock G.K., Allen S.J. Alpha- and beta-secretase: profound changes in Alzheimer's disease. Biochem. Biophys. Res. Commun., 2002; 6, 299(3):373- 376.
[25]. Vassar R. BACE1: the beta-secretase enzyme in Alzheimer's disease. J. Mol. Eurosci., 2004; 23(1-2):105-114.
[26]. Walldius G., Jungner I. Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. J. Intern. Med., 2004; 255(2):188-205.
[27]. Weiler M., Federica A., Canu E., Magnani G., Copetti M., Santangelo R., Falautano M., Comi G., Falini A., Filippi M. Brain structural changes in the course of Alzheimer's disease.2015; 84 (14 Supplement). http://n.neurology.org/content/84/14. Supplement/P6.214.
[28]. Winblad B., Graf A., Riviere M.-E., Andreasen N., Rya J. M. Active immunotherapy options for Alzheimer's disease. Alzheimer's Res. Ther., 2014; 6(1):7-12.
[29]. Yamazaki Yu, Painter M.M., Bu G., Kanekiyo T. Apolipoprotein E as a Therapeutic Target in Alzheimer's disease: A Review of Basic Research and Clinical Evidence. CNS Drugs, 2016; Sep. 30(9):773–789.