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INTRACELLULAR WAYS OF DEVELOPMENT OF ALZHEIMER'S DISEASE AGAINST THE BACKGROUND OF HERPES VIRAL INFECTIONS (literature review)

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Abstract. Intracellular ways of development of Alzheimer's disease against the background of herpes viral infections (literature review). Ostrovska S.S., Shatorna V.F. Liholetov E.O. *The concept of the viral etiology of Alzheimer's disease (AD) was first proposed in 1982. Its author MJ Ball suggested that the herpes simplex virus (HSV1) may be involved in the pathogenesis of AD, finding that the areas of the brain damaged in acute herpetic encephalitis are the same as those that are affected in AD, and those who survived usually suffer from memory loss and other cognitive impairment typical of AD. Subsequently, in all postmortem brain samples (temporal, frontal, and hippocampal) viral sequences of the viral thymidinekinase gene were found in a high proportion (70-100%) both in AD and in elderly people without it, while in young people and children the virus was found in very low proportions, so it was suggested that HSV1 comes from the peripheral ganglia, where the virus can remain inactive for many years, then enters the brain at an older age due to a decrease in the activity of the immune system. The increased risk of AD is associated with the presence of HSV1 in the brain and the carriage of a specific genetic factor – allele-ε4 of the apolipoprotein E4 gene (APOE-ε4). By themselves, neither HSV1 nor the APOE-ε4 allele were found as risk factors for the development of AD but their combination increased the risk of AD development by 12 times and made up 60% in patients with AD. The phenomena involved in the pathophysiology of AD are neurodegenerative changes that occur as a result of fibrillation and deposition of amyloid-β-peptide (Aβ) and neurofibrillary tangles – accumulations of aggregated phosphorylated tau-proteins (P-tau), leading to brain atrophy due to neuronal death. Traditionally, Aβ has been characterized as a catabolic by-product. However, it has recently been shown that Aβ-peptide has antiviral activity and protective effects against HSV infections in the brain. A 16-year study in Thailand with more than 33,000 patients showed that long-term use of antiherpetic drugs reduces the risk of dementia, including AD patients infected with HSV1. Patients with HSV1 infection who received antiherpetic drugs showed a lower risk of all types of dementia compared with the group without these drugs. Their positive effect on stopping the accumulation of amyloid beta and tau protein in the body has been confirmed. In this regard, it is assumed that vaccination against HSV1 may be useful not only for treatment, but also for the prevention of AD.*

Реферат. Внутриклеточные пути развития болезни Альцгеймера на фоне герпес вирусных инфекций (обзор литературы). Островская С.С., Шаторная В.Ф., Лихолетов Е.А. *Концепция вирусной этиологии болезни Альцгеймера (БА) впервые была предложена в 1982 году. Её автор M.J. Ball предположил, что вирус простого герпеса (HSV1) может быть вовлечен в патогенез БА, обнаружив, что области мозга, повреждённые при остром герпетическом энцефалите, такие же, как и те, которые поражаются при БА, а больные, пережившие энцефалит, обычно страдают от потери памяти и других когнитивных нарушений, типичных для БА. В последующем во всех посмертных образцах мозга (височная, лобная и гиппокампальная) были обнаружены вирусные последовательности гена вирусной тимидинкиназы в высокой пропорции (70-*

100%) как при БА, так и у пожилых людей без неё, при этом у молодых людей и детей вирус обнаруживался в очень низких величинах. Было высказано предположение, что HSV1 поступает из периферических ганглиев, где вирус может оставаться в неактивной форме в течение многих лет, затем поступает в головной мозг в более старшем возрасте, вследствие снижения активности иммунной системы. Высокий риск развития БА связан с наличием в головном мозге HSV1 и носительством специфического генетического фактора – аллеля-ε4 гена аполипопротеина Е4 (APOE-ε4). Сами по себе ни HSV1, ни аллель APOE-ε4 не были обнаружены как факторы риска развития БА, однако их комбинация увеличивала риск развития БА в 12 раз и составляла 60% у пациентов с БА. Феноменами, вовлеченными в патофизиологию БА, являются нейродегенеративные изменения, которые возникают в результате фибриллизации и отложения амилоид-β-пептида (Аβ) и нейрофибриллярных клубков – скопления агрегированных фосфорилированных тау-белков (P-тау), приводящие к атрофии мозга вследствие гибели нейронов. Традиционно Аβ характеризовался как катаболический побочный продукт. Однако недавно было показано, что Аβ-пептид обладает противовирусной активностью и защитными эффектами против HSV-инфекций в головном мозге. Шестнадцатилетнее исследование в Тайланде с участием более 33 000 пациентов показало, что длительное применение противогерпетических препаратов снижает риск развития деменции, в том числе у пациентов с БА, инфицированных HSV1. Больные с HSV1-инфекцией, получавшие антигерпетические препараты, показали пониженный риск всех типов деменции по сравнению с группой без лечения этими препаратами. Подтверждено их положительное влияние на прекращение накопления бета-амилоида и тау-белка в организме. В связи с этим предполагается, что вакцинация от HSV1 может быть полезной не только для лечения, но и для профилактики БА.

Among many factors responsible for the pathogenesis of Alzheimer's disease (AD), much attention is paid to the role of infectious agents, for example the development of AD under the action of various periodontal pathogens from the oral microbiome, resulting in persistent infection that penetrates the brain and damages nerve cells and vessels of the microcirculature [2]. However, numerous epidemiological, experimental data and clinical observations suggest that one of the main causes of AD is the constant recurrence of herpes simplex virus type 1 (herpes simplex virus 1 – HSV1) [10, 14, 16, 17, 21].

The concept of the role of viruses in the development of AD was first proposed several decades ago. It is known that the initial HSV1 infection usually occurs in early childhood and after infection the virus remains in a latent state throughout life in the nervous system with very limited transcription and with very low or zero protein synthesis. The author of the concept suggested that latent HSV1 can be reactivated in the peripheral ganglia and ascend along the known nerve pathways to the limbic system and areas of the brain that are most affected in AD [7]. The virus is prevalent in approximately 90% of the adult population, which is also associated with a high prevalence of AD. HSV1 reactivation can be periodically provoked by factors such as immunosuppression, peripheral infection or inflammation, and the cumulative damage to these brain injuries ultimately leads to the development of AD, mainly in the elderly [27].

In the brain of patients with AD pathognomonic lesions of neurons, especially in large numbers, occur within the limbic system, in the same temporal areas that are predominantly affected by HSV1 in acute herpetic encephalitis and those who experience it, usually suffer from memory loss and cognitive impairments typical of AD. This is evidence that HSV1 can be transported to the central nervous system (CNS) from the peripheral nervous system [13]. These data are confirmed by the fact that HSV1 receptors are selectively expressed in the limbic system [20]. A highly sensitive polymerase chain reaction (PCR) method was used in the human brain to search for HSV1 DNA, in particular the viral thymidine kinase (TK) gene. In all postmortem samples of the brain (temporal, frontal and hippocampal) viral sequences of TK in high proportions (70-100%) both in sporadic (non-hereditary) AD and in the elderly without AD were found. In young people and children, the virus was found in very low values, and therefore it has been suggested that HSV1 enters the brain of older people due to reduced activity of the immune system [15, 19]. A special risk of AD is the presence of HSV1 in the brain and the carrier of a specific genetic factor - the allele-ε4 of the apolipoprotein E4 gene (APOE-ε4). As shown in postmortem studies of the brain of patients with AD [5, 11], HSV-1 and the allele (APOE-ε4) alone, as a rule, cannot be independent risk factors for the development of AD. However, their combined effect increased this risk 12-fold [12] and was 60% in AD [5]. APOE genotypes were compared in 40 people with herpes recurrences and in 33 patients who did not suffer from this disease, the incidence of APOE-ε4 was 36% and 9%, respectively ($p<0.001$). These data also indicate that a strong provoking factor in the development of AD is the presence of HSV1 in the brain and the carrier of the

APOE-ε4 allele, and that their combined effect is the most damaging to the nervous system [5].

Studies in APOE-transgenic mice infected with HSV1 have also shown that animals with APOE-ε4 show a greater potential for viral damage. Mice were inoculated with HSV1 and the DNA concentration of the virus in the brain was measured. In thirty seven days after infection, the concentration of HSV1 DNA in the brains of wild-type APOE +/+ mice was 13.7 times higher than in mice with APOE - / -knock-out. The concentration of HSV1 DNA in the brain of transgenic mice with APOE-ε4 was 13.6 times higher than in mice with APOE-ε3. Apolipoprotein-ε4 obviously significantly facilitates the latency of HSV1 in the brain than apolipoprotein-ε3, and protein doses are directly correlated with the concentration of HSV1 in the brain. It was also shown later that apolipoprotein interacts with HSV1 in animal models, increasing the viral load in the brain. Thus, two-month-old wild-type knock-out mice were infected with HSV1 and were observed for 16 months. It was found that the viral load increases with age. In older female mice APOE + / + wild-type, HSV1 was by 43 times higher than in female mice APOE - / -. Although MRI did not show neuropathological and morphological differences in the brain between 18-month-old infected mice compared to controls, HSV1-infected mice had memory deficits and decrease in metabolic indices of the CNS health [8, 9]. These studies on animals link that APOE-ε4 with the increased HSV1 viral load in the brain confirm the above post-mortem studies in humans [5] and indicate that the combined presence of HSV1 in the brain and the carrier of the APOE-ε4 allele are involved in pathogenesis of HA. The APOE gene, or rather its form APOE-ε4, is very interesting and important of itself. It is present in every fourth person. The APOE gene encodes the protein apolipoprotein E, which is an important component of lipoproteins. It is synthesized mainly in the liver, in brain cells and regulates lipoprotein metabolism. Variants of the apolipoprotein E gene are well studied. All genes are represented by pairs, one from each parent. Thus, there are six possible combinations of alleles of the APOE gene: APOE: ε2/ε2, ε2/ε3, ε3/ε3, ε4/ε2, ε4/ε3, ε4/ε4. People who carry at least one copy of the ε4 allele have an increased risk of developing AD as compared to those without it. In the presence of two copies of ε4 (ε4/ε4), the risk of developing AD increases significantly than with one copy of ε4 [26]. In people with AD who were carriers of ε4, the level of APOE protein in the blood is lower [23], although low levels of APOE protein in plasma increase the risk of developing AD regardless of the APOE genotype [25]. The presence of the APOE-ε4 allele also affects the risk of cardiovascular disease. In the presence of at least one allele APOE-ε4 the likelihood of atherosclerosis increases. Carriership of APOE-ε4 is also associated with poor recovery from traumatic brain injury and stroke. Carriership of APOE-ε4 accelerates neurodegeneration and aging of blood vessels. In general, a tenfold increase in the risk of AD and a 40% increase in the risk of cardiovascular disease were found for the ε4/ε4 genotype. Knowledge of the genotype of APOE allows to assess the risk of pathological conditions and correctly determine the tactics of their prevention [1].

The most described phenomena involved in the pathophysiology of AD are neurodegenerative changes that occur as a result of fibrillation and deposition of amyloid-β-peptide (Aβ) in the form of β-amyloid and neurofibrillary tangles (NFT) - clusters of aggregated phosphoryls -tau), which macroscopically lead to brain atrophy due to neuronal death [3]. Traditionally, Aβ has been characterized as a non-functional catabolic by-product. However, Aβ has recently been identified as an antimicrobial peptide (AMP), and that Aβ deposition may be a protective innate immune response to infection. The physiological role of Aβ as AMP also coincides with the surprisingly high conservation of the peptide in evolution. Human Aβ is at least 400 million years old and is found in 60-70% of vertebrate species [24]. It is shown that Aβ has, among other things, antiviral and protective action against HSV virus in the brain, preventing the fusion of the virus with the plasma membrane, and the infection can not only initiate but also dramatically accelerate the deposition of β – amyloid. In AD, normal protective antimicrobial pathways mediated by Aβ oligomerization are overactive, and subsequent Aβ deposition causes neuroinflammation, leading to neuropathology and widespread neuronal death [4]. Aβ-mediated antiviral activity was tested in encephalitis models in transgenic mice (5XFAD) and models of infections on cell cultures. It has been shown that Aβ-oligomers bind surface glycoproteins of the herpes virus, accelerating the deposition of β-amyloid. These data support the idea that Aβ may play a protective role in innate CNS immunity, and confirm the etiological mechanism of AD, in which herpes viridae infection can directly stimulate Aβ amyloidosis. Aβ oligomers have also been shown to bind and agglutinate HSV1 and HHV6 viruses and identify herpes viridae envelope glycoproteins as targets for binding. Aβ-oligomers, thus, serve as a congenital mediator of the internal

stability of the CNS, protecting the brain from herpes viral infection [4].

Neuroglioma (H4) cell cultures were used as in vitro model to investigate whether Aβ is produced by neuroglioma cells and whether this may lead to protective activity against HSV1 infection. The results showed that H4 cells secrete Aβ in response to HSV1 infection. In addition, the combination of Aβ and HSV1 induced the production of anti-inflammatory cytokines TNFα, IL-1β and IFNα in cell lines. Antiviral protection of Aβ was also found in experiments using a conditioned medium that provided Aβ-dependent protection against HSV1 replication in cultures of de novo H4 cells infected with HSV1. H4 neuroglioma cells produced Aβ in response to HSV1 infection by inhibiting secondary replication of the virus. This mechanism may play a role in the etiology of HA [24].

Changes found in cultures of HSV1-infected cells have also shown that reactivated HSV1 can cause increased formation of Aβ and P-tau, with HSV1 DNA specifically localized in amyloid plaques [17, 28]. For herpes viral infections in humans, the protection of the brain provided by the uptake of viral particles by the Aβ-peptide carries a long-term risk of developing pathogenic β-amyloidosis, which is characteristic of AD. Possible factors contributing to the transition from protective to neuropathological Aβ deposition include virulence and persistence of the pathogen itself, as well as host genetics and environmental factors. The neuropathogenesis of AD mediates innate Aβ immune pathways targeting viral pathogens, which is consistent with the amyloid cascade hypothesis and data showing the role of Aβ in AD pathology [4].

A 16-year study of more than 33,000 patients showed that long-term use of antiherpetic drugs reduced the risk of developing dementia, including in patients with AD infected with HSV1. Patients with HSV1 infection receiving antiherpetic drugs showed a reduced risk of developing all types of dementia, such as AD, VAD (vascular dementia) and a number of others, as compared to the group without treatment with these drugs. In general, patients with short (<30 days) or long-term (≧ 30 days) treatment with antiherpetic drugs had a reduced risk of developing dementia, and the duration of treatment directly reduced the risk of developing dementia [6]. Acyclovir, penciclovir, or foscarnet are usually prescribed to prevent HSV1. The positive effect of these drugs on the cessation of Aβ and tau protein accumulation in the body has been confirmed [18]. In this regard, it is assumed that vaccination against HSV1 may be useful not only for the treatment but also for the prevention of AD. The role of antiherpetic drug treatment for the prevention of AD has not been studied in the past, although the founder of the viral concept of AD has argued that antiviral drugs in neurodegenerative diseases may be a new paradigm aimed at treating AD [7]. In recent years, the effectiveness of potential drugs for the treatment of AD has been actively studied. In Sweden, for example, valacyclovir (valaciclovir) is used to treat patients with AD. This is an open-label pilot study in which 36 participants received the drug for 4 weeks. The dose was 500 mg three times a day in the first week and 1000 mg three times a day for the next 2-4 weeks. Important criteria for inclusion of patients in the study are the carrier of HSV1, allele ε4 of the apolipoprotein E4 gene and sufficient renal function (expected glomerular filtration rate above 30 ml/min). Participants were examined using a variety of techniques before and after treatment, including: minipsychotic status to assess cognitive function, cerebrospinal fluid biomarkers, positron emission tomography/computed tomography to detect active HSV1 infection in the CNS [22].

CONCLUSIONS

Thus, significant data have been accumulated to support a causal relationship between HSV1 reactivation in the CNS and AD-like decline in cognitive function, as well as the fact that recurrent HSV1 infection in the brain plays a critical role in pathogenesis of AD, directly activating intracellular pathways leading to the development of AD. It is concluded that the connection of HSV1 with AD is already greater than the hypothesis [14], and therefore it is necessary to pay more attention to infectious and especially viral agents among environmental factors that contribute to the pathogenesis of AD.

Conflict of interests. The authors declare no conflict of interest.

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