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THE RELATIONSHIP BETWEEN SCHIZOPHRENIA AND ALZHEIMER'S DISEASE - AN ATTEMPT TO A HOLISTIC VIEW OF NEURODEGENERATIVE DISORDERS

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ABSTRACT

Schizophrenia and Alzheimer's disease are serious neurological disorders that, despite their different clinical pictures, show significant connections at the neuroanatomical, genetic, and functional levels. Research suggests that patients with schizophrenia have an increased risk of developing dementia, including Alzheimer's disease. Neuroimaging analyses indicate similarities in white matter damage, reduction in the volume of the hippocampus and prefrontal cortex, suggesting common neurodegenerative mechanisms that lead to cognitive impairment and behavioral changes. Genetic studies show a partial overlap in the polygenic risk of schizophrenia and Alzheimer's disease, especially in the genes related to neurotransmission, neuroinflammation, and synaptic function. Furthermore, the occurrence of psychotic symptoms in Alzheimer's disease may have different mechanisms than in schizophrenia, which significantly affects the effectiveness of therapy. Second-generation drugs, such as risperidone or aripiprazole, exhibit varying effectiveness depending on the neuropathological basis of psychosis, which underscores the need for individualized therapy and the search for new treatment strategies. New research directions focus on identifying neurodegenerative biomarkers and innovative therapeutic methods. There is particular hope for anti-PD-1 immunotherapy, which can modulate the inflammatory response and slow the progression of Alzheimer's disease. Additionally, the development of liquid biomarkers and advanced neuroimaging studies may enable earlier detection of pathological changes, which will allow for more effective therapeutic intervention.

KEYWORDS

Schizophrenia, Alzheimer's Disease, Dementia, Therapeutic Strategies, Biomarkers

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Is there a connection between schizophrenia and dementia?

Emil Kraepelin, a German psychiatrist, called by many the father of modern psychiatry, introduced the term dementia praecox, or "early dementia," into the nomenclature at the end of the 19th century as a set of cognitive, emotional, and volitional disorders with an unfavorable course, leading to gradual mental degradation [1,2]. This is considered one of the first descriptions of the symptomatology of the disease known today as schizophrenia. It may be thought-provoking to consider the connection between dementia and psychotic disorders in retrospect. According to Kraepelin, the primary symptom of dementia praecox was the fading of affect, which is now recognized as a component of the negative symptoms of schizophrenia.

Both dementia and schizophrenia are serious health problems - despite their different prevalence in the population (schizophrenia - about 1%, dementia - 5-10% of people between 60 and 70 years old and even 25% in higher age ranges) they cause significant impairment of individuals' functioning in society.

Despite separate classifications in ICD-10 and ICD-11, both of these diseases can be classified as neurodegenerative disorders (or, in the case of schizophrenia, as disorders with a neurodegenerative component). Dementia as a result of natural changes in the brain that occur with age, and schizophrenia as a disorder that probably has its roots in the perinatal period and progresses over time. Their common denominator appears to be the presence in the symptomatology of cognitive function disorders, which was already noticed in the 19th century as a primary symptom of various forms of dementia and as a negative symptom of schizophrenia. It is also worth adding that dementia involves disturbances in perception and thought content - hallucinations and delusions, which are among the basic symptoms of schizophrenia.

The development of technology has enabled tracking structural changes in the brain, such as in schizophrenia: enlargement of the lateral ventricles (decrease in gray and/or white matter volume), decrease in overall brain volume, decrease in hippocampal volume, decrease in temporal lobe volume, enlargement of the basal ganglia (mainly as a result of treatment), decrease in thalamic volume, decrease in cerebral cortex volume (mainly frontal and temporal lobes), and reduction in cortical folding. However, changes in dementia: significant enlargement of the lateral ventricles (decrease in gray and white matter volume), enlargement of the sulci and brain spaces, decrease in hippocampal volume, reduction of hemispheric asymmetry. It is worth noting the

similarities - reduction in the volume of nervous tissue in both gray and white matter, reduction in the hippocampus - resulting in characteristic symptoms (especially memory loss and neurobehavioral changes) [1].

Meta-analizes show a significant relationship between schizophrenia and the risk of developing dementia. Individuals with schizophrenia have a higher risk of developing dementia than the general population. It also turns out that the risk is higher for women than for men. This may be due to several reasons. First, women are more likely to be lonely in old age because men live shorter lives. Another reason may be the lowered level of estrogen after menopause, which has a protective effect on the CNS. It is associated with reduced cognitive functions, particularly short-term memory. A known risk factor for dementia is the APO E4 allele, which poses a greater risk for women than men (especially for homozygotes). One reason may also be that women are more prone to mood swings, insomnia, anxiety disorders, and depression, which alter brain function in a way that can cause dementia to progress.

There is evidence that cognitive changes occur in schizophrenia at the beginning of the disease, just as they can occur during a typical neurodegenerative disease. Behavioral and cognitive changes in schizophrenia are in some cases so severe that they can meet the diagnostic criteria for dementia [3]. In terms of cognitive function, 50- and 60-year-old individuals with schizophrenia performed similarly to healthy individuals aged 70-80 in tests of information processing speed and verbal episodic memory. Age differences are more pronounced in individuals with schizophrenia older than 70 [4].

The cause of dementia in people with schizophrenia is not known, although there are some explanations. First, patients with schizophrenia are more prone to many chronic diseases, such as cardiovascular disease, addiction, atrial fibrillation or flutter, superficial vascular disease, diabetes, all of which are also risk factors for dementia [3]. Subsequently, the pathophysiology of schizophrenia is associated with dysfunction of memory and cognitive functions, which leads to brain dysfunction and typical changes in neuroimaging. Third, it is possible that both diseases have a common etiology. Finally, the higher risk may also be explained by the use of neuroleptics and their side effects. A 9-year observational study showed that multimodal antipsychotic therapy caused changes in cognitive functions, such as verbal learning and memory (Husa et al., 2014) [6].

The problem shown in the research is that people with schizophrenia have a shorter life expectancy than the population, so it is not possible to observe many patients in terms of dementia, because they live shorter lives - as the data says even 10 to 15 years [1].

It is worth mentioning the result of a cohort study conducted in Denmark from 1995 to 2013 on 2,845,440 people over the age of 18. 20,683 had previously suffered from or had been diagnosed with schizophrenia. 136,012 developed dementia, of whom 944 had a history of schizophrenia. Schizophrenia was associated with more than double the risk of dementia, including a 4-fold increased risk of dementia in those younger than 65 years. 7.4 out of 100 people with schizophrenia developed dementia before the age of 80, compared to 5.8 out of 100 people in the general population. Attention was drawn to the co-existing diseases I mentioned earlier, with a strong emphasis on addiction to various types of substances - in people with schizophrenia, this was a strong risk factor for developing dementia [4].

The difficulty for researchers seems to be the different age of onset for both diseases - the average age of onset for schizophrenia in the study was 28 years, and for dementia 81 - it is difficult to build studies with the appropriate follow-up time to demonstrate a proper cause-and-effect relationship between both diagnoses [5].

Because schizophrenia is associated with pre-existing cognitive dysfunction, such individuals may experience symptoms suggestive of dementia earlier than those without schizophrenia. However, according to the definition of dementia, a loss of cognitive function is required compared to the state before the onset of symptoms.

Neuroanatomical and genetic links between schizophrenia and dementia, and antipsychotic treatment

One should address the macroscopic scale of the problem - disorders concerning white matter and neuronal pathways that function abnormally in the course of both diseases. The dominant pathways in the etiology of schizophrenia and AD do not overlap, although in both cases we are dealing with a profound impairment of white matter - even before the onset of symptoms. In the work of Kochunov et al. [7], the RVI (regional vulnerability index) parameter was used. It quantifies the similarity between the patterns of the subject's white matter and the patterns characteristic of AD. It is calculated as a comparison of FA (fractional anisotropy) in 22 white matter regions in a patient with expected AD changes in the same regions. Higher RVI values in patients with schizophrenia would mean greater similarity in white matter deficits to those observed in AD. A significant correlation was observed in the patterns of white matter damage in both disorders studied, which was associated with cognitive impairment. This refers to associative pathways - reduction in areas such as ACR (anterior corona radiata), FX (fornix), GCC (genu of corpus callosum) and BCC (body of corpus callosum) commissural fibers. However, the damage does not include the motor and sensory pathways, such as the corticospinal tracts or the posterior root of the spinal nerve. ACR, GCC, and BCC contain the basic fibers connecting the ipsilateral and contralateral prefrontal cortex - they are crucial for higher cognitive functions. The FX is an associative fiber connecting the hippocampus with the lateral part of the hypothalamus and the frontal lobes. It is worth noting that the hippocampus atrophy is one of the main characteristics of AD disorders, while in schizophrenia it shows the greatest reduction of all subcortical regions. Higher RVI-AD in patients with schizophrenia indicate negative interactions between risk factors and white matter aging. Neuroimaging studies have shown similarities between AD and schizophrenia. For example, in both diseases, the anatomical integrity of the temporal lobes and hippocampal regions is disrupted.

In AD, white matter deficits may be secondary to beta-amyloid and APP accumulation in the neurons of the frontal and temporal cortex, which may affect the associative pathways of both regions. In schizophrenia, damage to pathways may result from incorrect gene expression in oligodendrocytes and their intracellular dysfunction. It is worth mentioning that the leading white matter has high metabolic requirements and is sensitive to any ischemic incidents. Patients with schizophrenia have a shorter average lifespan, and the main cause of their premature deaths is cardiovascular disease. Similarly, white matter vascular injury is a risk factor for AD, which would fit the two-hit theory - where the first hit is a metabolic disturbance resulting from neuronal ischemia, and the second is the accumulation of beta-amyloid.

Psychosis in the course of AD is an important issue. They can be partially explained by structural changes in the brain, such as: accumulation of hyperphosphorylated tau protein in various frontal regions and macrostructural and functional changes in frontal, parietal, and striatal regions [8]. Serra et al. [9] demonstrated a correlation between the volume of the right hippocampus and the middle frontal gyrus and the severity of psychosis. Moreover, patients with AD and hallucinations have stronger connections in the frontal regions and weaker connections in the left inferior parietal lobules. Hallucinations in AD have also been linked to the atrophy of the cortex of the parahippocampal gyrus and to reduced volume and metabolism in the right insula, the upper part of the temporal lobe, and the prefrontal areas. Such instability may be due to the fact that different psychotic symptoms may be the result of different neuropathological processes and potentially unrelated to AD, such as the presence of Lewy bodies, vascular damage, and leukoencephalopathy. In patients with AD and psychosis, it is suggested that the connections between the medial temporal lobe and the OFC (orbitofrontal cortex) are disrupted, similar to schizophrenia. A combination of severe medial-temporal atrophy, mainly due to AD pathology, but also potentially influenced by schizophrenia risk, and preserved OFC/mPFC (medial prefrontal cortex) volume is associated with a higher polygenic risk for schizophrenia.

The Manca et al. team conducted a study on 601 people, 211 of whom were a control group and the rest were diagnosed with MCI (mild cognitive impairment) or AD-related dementia [8]. The AD group was then divided into those with and without psychotic symptoms. The AD-PS (AD-psychosis) group was significantly older than the HC (healthy control) and AD-NP (AD-non-psychosis) groups and had lower education levels than the HC group. Sex differences were also noticeable - there were more men in the AD-PS group. An important correlation was the presence of the APOE ε4 genotype, which was much stronger in the AD-PS group. In neuroimaging analysis, bilateral atrophy of the medial and right-sided middle temporal regions was observed in AD-PS patients. Genetic analysis suggests that the risk of psychosis in AD may be primarily associated with genetic burden in AD, mainly referring to the APOE ε4 allele. The difference between the AD-PS group and the SCZ (schizophrenia) group was a change in the volume of gray matter - in AD, atrophy of

the left frontal regions, and in SCZ, a larger volume of the OFC/mPFC and a lower volume in the right-sided medial temporal regions and the globus pallidus. One of the study's conclusions is that dysfunction in the connections between the medial-temporal region and the OFC, and their trophic changes in both the SCZ and AD-PS groups, may play a major role in the manifestation of psychotic symptoms in AD patients.

However, focusing on genetic risk factors among the AD and SCZ populations, the study by Chen et al. demonstrated through a GWAS that the polygenic risk score (PRS) for AD is positively correlated with schizophrenia [10].

Several key genes and chromosome regions associated with the pathogenesis of schizophrenia have been identified [11]. COMT: Polymorphisms in COMT are associated with the risk of developing schizophrenia. DRD2: gene encoding the dopamine receptor type 2, which is crucial for dopaminergic neurotransmission. NRG1 (Neuregulin 1): plays a role in the development and functioning of the nervous system. DISC1 (Disrupted in Schizophrenia 1): associated with the development and functioning of neurons. GRIN2A (NMDA-type glutamate ionotropic receptor subunit 2A): encodes the subunit of the NMDA receptor, which is crucial for synaptic plasticity and cognitive function. CACNA1C (Calcium Voltage-Gated Channel Subunit Alpha1 C): important for neuronal signal transmission. ZNF804A (Zinc Finger Protein 804A): involved in regulating the expression of other genes. SETD1A (SET Domain Containing 1A): gene encoding a protein involved in histone methylation and gene expression regulation. These genes and their associated biological mechanisms help explain the complex pathophysiology of schizophrenia, including the disorders of neurotransmission, neuroplasticity, and neuronal development.

On the other hand, the genes associated with Alzheimer's disease (AD) are mainly those that affect the metabolism of amyloid beta and tau proteins, which form plaques and neurofibrillary tangles, characteristic of this disease. Here are some of the key genes associated with AD: APP (Amyloid Precursor Protein): encodes amyloid precursor protein, which is cut into smaller fragments, including amyloid beta, which forms amyloid plaques in the brain. PSEN1 and PSEN2 (Presenilin 1 and 2): encode presenilin proteins, which are part of the gamma-secretase complex, responsible for cutting APP into amyloid beta. Mutations in these genes are associated with early onset AD. APOE: wariant epsilon 4 (ε4) tego genu jest silnym czynnikiem ryzyka późnego początku choroby Alzheimera. APOE is involved in lipid metabolism and may influence the accumulation of amyloid beta in the brain. TREM2 (Triggering Receptor Expressed on Myeloid cells 2): Mutations in this gene are associated with an increased risk of AD. TREM2 is involved in the brain's immune response. CLU (Clusterin): involved in the removal of amyloid beta and its accumulation. PICALM (Phosphatidylinositol Binding Clathrin Assembly Protein): uczestniczy w procesie endocytozy, który może wpływać na metabolizm amyloidu beta. CR1 (Complement Receptor 1): plays a role in the immune system, and its variants are associated with the risk of AD. SORL1 (Sortilin-Related Receptor): involved in the transport of proteins and may affect the level of amyloid beta in the brain.

Research indicates that the polygenic risk score (PRS) for schizophrenia may influence the occurrence of psychotic symptoms in Alzheimer's disease. For example, PRS for schizophrenia correlates with smaller volumes of structures in the temporal area and larger volumes in the frontal area in patients with AD and psychotic symptoms. In the context of genetics, there are some connections between schizophrenia and Alzheimer's disease, which indicate that common genes may be relevant to both conditions. APOE ε4: a strong risk factor for late-onset Alzheimer's disease (AD). COMT: Polymorphisms in the COMT gene were associated with a higher risk of psychosis in Alzheimer's disease. Alpha 7 nicotinic receptor (CHRNA7): genetic variations in the alpha 7 nicotinic receptor were associated with delusional symptoms in AD. 16p11.2: rare duplications were identified in patients with psychosis in Alzheimer's disease.

Patients with AD who experience psychotic symptoms may benefit from other medications than those typically prescribed by clinicians. Sweet et al. conducted a genome-wide association study (GWAS) to identify risk loci for AD-PS compared to AD-NPS. The study compared the genetic correlations between AD-PS and AD, ALS (amyotrophic lateral sclerosis), PD (Parkinson’s disease), SCZ (schizophrenia), depression, and BPD (bipolar disorder). AD-PS showed a positive correlation with depression, but not with AD or schizophrenia [12].

It follows that AD-PS is not genetically related to schizophrenia, despite the overlap of some symptoms. Therefore, by identifying similarities and differences between the mechanisms, we can better understand the value of neuroleptic treatment in AD-PS. Using genetic databases, 975 genome-related changes and 1077 DEGs (differentially expressed genes) for AD-PS were found in relation to AD-NPS. 1668 genome-related changes and 464 DEGs were identified for schizophrenia. 1607 and 2123 unique genes were identified as related to AD P and schizophrenia. However, only 148 genes were common to both conditions. To examine

how neuroleptics affect the neuronal pathways in AD-PS and schizophrenia, several well-known second-generation drugs were selected: aripiprazole, olanzapine, quetiapine, and risperidone. All LDG (second-generation drugs) act on the DRD2 and HTR2A receptors as their main targets. Of the identified pathways, a strong association with inflammatory responses can be observed, as well as an association with autophagy and apoptosis. Because HTR2A and DRD2 are the most well-known targets of antipsychotic drugs and are involved in many biological processes that play a key role in neurological activity, the difference in their later effects can tell us a lot about how patients respond differently to medications. The results of the analysis of these pathways suggest a close relationship between AD P and neuroinflammation. In fact, AD P appears to be more correlated with depressive symptoms than with schizophrenia, suggesting the possibility of different mechanisms behind psychotic symptoms in AD P and schizophrenia. The primary targets of antipsychotic drugs show less efficacy in AD P than in SCZ, indicating that the interaction of antipsychotic drugs with these receptors may be less effective in modulating AD P.

In terms of efficacy, four LDGs suggest risperidone > aripiprazole > olanzapine > quetiapine. Three antipsychotic drugs, sertindol, fluphenazine, and ziprasidone, showed higher efficacy than risperidone, which is the most effective and most commonly used LDG. Sertindol and zyprazadone provide better efficacy and safety profiles in the treatment of psychosis. Previous studies also showed that sertindol has better efficacy than other LDGs in cognitive functions such as processing speed and executive functions, while zyprexa has better performance in situation assessment, executive functions, and processing speed, working memory, long-term memory, and verbal learning.

The identified neural pathways indicate a special role of neuroinflammation and RNA synthesis in AD P compared to schizophrenia. The study results showed that although inflammatory processes occur in both diseases, different forms of immune response can be activated in patients with AD P and schizophrenia and can be used to explain the causal relationship between systemic inflammatory response and the development of neuropsychiatric symptoms in AD.

A new perspective on the treatment of Alzheimer's disease and attempts to find biomarkers of psychosis in AD

Recent research offers hope for finding specific markers whose measurement can indicate those at risk of a more severe course of Alzheimer's disease. At the same time, dozens of studies are being conducted to improve treatment for those who have already been diagnosed. Interesting results have been obtained from research on immunotherapy, particularly with antibodies against PD-1.

The role of markers in medicine has been established for a long time, and they are mainly associated with inflammatory conditions and cancer - in these situations, they are used on a daily basis. However, it is worth considering looking for specific proteins or genes that would help to some extent predict whether a person at risk of developing dementia may experience negative symptoms such as psychosis. Haque et al. in their work presented a panel of 48 proteins detected in cerebrospinal fluid that can serve as such biomarkers [13]. Among 48 proteins, the concentration of 18 of them was significantly increased in AD, while 4 were significantly decreased. It was found that the most abundant proteins and strongest AD classifiers in the CSF 48 panel were the proteins activating the zeta (YWHAZ) and beta (YWHAB) tyrosine 3-monooxygenase/5-monooxygenase of tryptophan, and the 14-3-3 proteins. These proteins have been previously linked to AD and Creutzfeldt-Jakob disease (CJD) in cerebrospinal fluid and are associated with many aspects of brain function, including neuronal signaling, synaptogenesis, and neurodifferentiation. Increased SMOC1 levels were also shown to be associated with SPARC, a protein previously identified as a matrix-associated co-expression module (MACM) protein with the strongest association with global AD pathology in post-mortem brain studies. Moderate increases were also observed in pyruvate kinase M1/2 (PKM1/2), malic enzyme 1 (MDH1), enolase 1 (ENO1), fructose-bisphosphate aldolase A (ALDOA), proteins key to glycolysis, gluconeogenesis, and the citric acid cycle. The proteins that were most reduced in the cerebrospinal fluid from AD were VGF and secretogranin II (SCG2), neurosecretory granins involved in axonal transport or synaptic vesicles, and NPTXR and NPTX2, proteins involved in glutamatergic synaptic transmission and involved in synaptic plasticity and memory.

The study also used PET-FDG and MRI to confirm that the proteins are associated with altered glucose metabolism in the brain and reduced hippocampal volume seen in MRI. It was discovered that 20 proteins in the CSF 48 panel were associated with FDG-PET and 15 proteins were associated with both FDG-PET and hippocampal volume. The CSF analyte most strongly associated with FDG PET and hippocampal volume was

CSF Aβ42. Both FDG PET and hippocampal volume were positively correlated with the reduction of synaptic proteins in AD, neuronal pentraxin 2, neuronal pentraxin receptor, VGF, and SCG2. FDG PET and hippocampal volume were negatively correlated with CSF pTau181, CSF tTau, YWHAZ, YWHAB, and to a lesser extent, SMOC1.

In the study, the CSF 48 panel accurately predicted the pathophysiology and AD disease in the fluid as well as or better than the known AD biomarkers in CSF, Aβ42, tTau, and Tau181, and the panel provided additional diagnostic and prognostic utility. Interestingly, the CSF 48 panel generally showed better performance in predicting baseline AD imaging biomarkers (FDG PET, hippocampal volume, and AV45 SUVR) and measures of cognitive function and dementia severity (MoCA and CDR-SB). Moreover, when the CSF 48 panel was combined with the canonical AD CSF biomarkers, improved predictive capabilities were observed. It is worth noting that the CSF 48 panel demonstrated the ability to predict annual changes in cognitive function (MoCA), dementia severity (CDR-SB), and neurodegeneration (hippocampal volume, FDG-PET) as well as or better than traditional AD CSF biomarkers and additive improvement compared to existing AD CSF biomarkers alone.

Ismail et al. conducted an even more detailed study on psychosis in the course of AD [14]. Several genes have been identified in its course, the identification of which could help us predict the course of the disease, and more specifically the possibility of psychotic symptoms, which, as we know, are a factor in a worse course of AD. Psychosis in Alzheimer's disease is a complex phenomenon influenced by both genetic and epigenetic factors. Among others: ENPP6 - a gene that codes for a protein involved in phospholipid metabolism, which is crucial for neuronal function. He was deemed to be at risk of psychosis in AD. This suggests that changes in lipid metabolism may influence neurodegenerative and neuroinflammatory processes in the brain, leading to psychotic symptoms. SUMF1 encodes a protein responsible for activating sulfatases, enzymes involved in the degradation of sulfates, which are important for various biological processes, including brain development and neuronal function. This is a gene associated with a lower risk of psychosis in AD, suggesting that sulfatase functions may protect against the pathological processes associated with psychosis in AD. APOE ε4 - associated with a small but statistically significant increase in the risk of psychosis. GBA encodes glucocerebrosidase, an enzyme that breaks down glucocerebroside in lysosomes. In the case of Parkinson's disease, mutations in the GBA gene double the risk of psychosis. It is also associated with psychosis in dementia with Lewy bodies. TBX15 is a transcription factor involved in various developmental processes, including tissue and organ development. Hypomethylation in this gene is consistent in the prefrontal cortex, the superior temporal gyrus, and the entorhinal cortex in individuals with AD psychosis. WT1 encodes a protein that functions as a transcription factor and plays a role in regulating cell growth and development. Its hypomethylation is also consistent in the same areas of the cortex as in the case of TBX15 in people with psychosis in AD.

The triggers of psychosis in Alzheimer's disease are complex and multifactorial. According to Ismaila et al. (2022), several key factors contribute to the occurrence of psychotic symptoms in people with AD. Both genes associated with schizophrenia risk and AD have been shown to be involved in psychosis in AD. Specifically, hyperphosphorylated tau protein burden and calyculin-mediated synaptic dysfunction are considered biological components of psychosis in AD. Psychosis in AD is also related to the stage and progression of the disease. Delirium and hallucinations in AD differ depending on the patient's characteristics, with delirium being associated with advanced dementia and longer disease duration. Neuropathological studies have shown that the presence of psychosis in people with AD was associated with the presence of Lewy bodies, suggesting a degree of overlap between amyloid pathology and synucleinopathy. Psychosis in AD may coexist with other neuropsychiatric symptoms, such as agitation, depression, and anxiety, which can further complicate the clinical picture. New diagnostic criteria developed by the International Psychogeriatric Association (IPA) and the Alzheimer's Association (ISTAART) help better understand and classify psychosis in AD, which can lead to better identification and treatment of these symptoms in the context of neurodegenerative disease. In summary, the triggers of psychosis in AD include a combination of genetic, biological, and disease stage factors, as well as the presence of other neuropsychiatric symptoms. Modern diagnostic and research approaches help in better understanding these mechanisms, which can lead to more effective treatment strategies.

Recent research has begun to point to a problem much deeper than beta-amyloid aggregation and the presence of hyperphosphorylated tau. The theory of neuroinflammation and the possibility of using our immune system to restore the normal functioning of neurons began to gain ground. It turned out that systemic immunity should be strengthened, not suppressed, in order to stimulate the immune system-dependent cascade

necessary for brain repair. One promising treatment is immunotherapy using PD-1 checkpoint blockade [15,16]. In the context of neurodegenerative diseases, PD-1 blockade induces a systemic IFN-γ-dependent immune response that enables the mobilization of monocyte-derived macrophages to the brain. This process resembles the tissue-specific immune surveillance induced by the blockade of immune checkpoints in cancer therapy. Treatment with PD-1 blockade reduced the burden of Aβ plaques in the brain in two mouse models of AD in advanced stages of the disease. The study also indicates that changes in PD-1/PD-L1 expression on peripheral T cells may correlate with different stages of Alzheimer's disease, suggesting the possibility of using this therapy in specific stages of the disease. Immunotherapy using PD-1 blockade appears to be a promising strategy in the treatment of Alzheimer's disease, particularly in the context of reducing neuroinflammation and improving cognitive function. However, further clinical trials are needed to determine its effectiveness and safety in humans.

Ghareghani et al. in their study emphasize the role of NOD2 receptors, which are key to the body's immune response, recognizing fragments of bacterial peptidoglycan and activating signaling proteins that stimulate the production of pro-inflammatory cytokines [17]. Activation of NOD2 by muramyl dipeptide (MDP) converts inflammatory monocytes into patrolling monocytes that have a greater ability to phagocytose and remove vascular amyloid associated with AD. Another study by Grabert et al. (2016) examined the role of monocyte patrolling in Aβ phagocytosis [18]. It has been shown that patrolling monocytes are the main phagocytic cells responsible for removing Aβ from the brain, suggesting that these cells may play an important role in the pathogenesis of AD. The recruitment of monocytes to amyloid deposits in blood vessels is not fully understood, but CCR2, CCR5, and CX3CR1 are thought to be partially involved in their recruitment. It was also discovered that MDP-stimulated NOD2 was associated with increased expression of the Aβ transporter, a protein associated with the low-density lipoprotein receptor (LRP-1). LRP-1 transports Aβ from the mucous membrane to the lumen of the blood-brain barrier (BBB), where patrolling monocytes can capture it. In summary, it was found that a better strategy in the treatment of AD is to utilize the potential of monocyte patrolling to absorb vascular-cerebral Aβ instead of using methods aimed at blocking the formation of Aβ plaques.

Mukherjee et al. (2024) divide immunotherapy in AD into passive (monoclonal antibodies) and active (antigen-specific vaccines) [19]. The text also describes immunotherapy focused on the tau protein, including both active vaccines and passive antibodies that target specific regions or sites in the tau protein. Another target for immunotherapy may be TREM2, an immune system receptor that is involved in the pathogenesis of AD. Mutations in the TREM2 gene are associated with an increased risk of developing the disease. Individuals with such mutations have reduced protein functionality, which leads to weakened microglial activation, reduced phagocytosis, and increased accumulation of amyloid beta. Antibodies that bind to TREM2 receptors can activate signaling pathways in immune cells, which potentially improves the function of microglia and supports the elimination of pathological proteins in AD. An example of such a therapy is the monoclonal antibody IgG AL002 (Alector; AbbVie). Immunization with AL002 in transgenic mice led to increased influx of microglia in the hippocampus and cortex and reduction of amyloid deposits.

Conclusions

New research brings hope - both for faster diagnosis of AD patients and for predicting the course of the disease - the CSF 48 panel has shown us valuable biomarkers, the detection of which may be the future of dementia care. For those diagnosed, a great hope is the large number of studies being conducted on immunotherapy - possibly the first path of causal treatment, not just symptomatic treatment of Alzheimer's disease. The results of the presented research are promising, but it should be remembered that translating results from mouse models to humans may involve additional problems that scientists will have to deal with. Many of the antibodies currently being tested have already passed the first phases of clinical trials, and the results of some of them are promising [20].

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