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Genetic and epidemiological factors in the pathogenesis of neurodegenerative disorders

Czynniki genetyczne i epidemiologiczne w patogenezie zaburzeń neurodegeneracyjnych

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Abstract

The aim of this study was to present the current knowledge on the aetiopathogenesis of neurodegenerative disorders, devoting attention not only to neurophysiological and clinical aspects, but above all to the genetic and extra-genomic conditions underlying these diseases. The dynamic development of knowledge and technological progress in medical and related sciences is resulting in changes in the demographic structure of the human population (ageing populations). One of the consequences of these changes is an increase in the incidence of neurodegenerative disorders. Neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, and Huntington's disease. They belong to a group of disorders whose common feature is a pathological process leading to the loss of nerve cells through apoptosis or necrosis. The aetiology of neurodegenerative diseases is multifactorial and, in addition to the involvement of genomic factors, extra-genomic mechanisms have been postulated to be involved in their aetiopathogenesis. The aetiology of numerous neurodegenerative diseases is still not fully understood. Therefore, intensive research has been ongoing for years, focusing, among other aspects, on the causes and course of such conditions. An important direction of research into the pathogenesis of neurodegenerative diseases is assessment of their potential genetic aspect. Many studies also focus on non-genomic factors, highlighting that many of them can have a significant impact on the course of these diseases.

Keywords: genetic factors, neurodegenerative disorders, extra-genomic conditions

Streszczenie

Celem pracy było przedstawienie aktualnego stanu wiedzy na temat etiopatogenezy zaburzeń neurodegeneracyjnych, ze szczególnym uwzględnieniem aspektów neurofizjologicznych i klinicznych oraz, przede wszystkim, uwarunkowań genetycznych i pozagenomowych leżących u podstaw tych schorzeń. Dynamiczny rozwój wiedzy i postęp technologiczny w naukach medycznych i pokrewnych skutkuje zmianami w strukturze demograficznej populacji ludzkiej (starzenie się społeczeństw). Jedną z konsekwencji tych zmian jest wzrost zachorowalności na choroby neurodegeneracyjne, w tym chorobę Alzheimera, chorobę Parkinsona i chorobę Huntingtona. Należą one do grupy chorób, których wspólną cechą jest patologiczny proces prowadzący do utraty komórek nerwowych w wyniku apoptozy lub martwicy. Etiologia chorób neurodegeneracyjnych jest wieloczynnikowa – w ich etiopatogenezie oprócz udziału czynników genomowych postuluje się również udział czynników pozagenomowych. Przyczyny wielu chorób neurodegeneracyjnych znane są wciąż tylko częściowo. W związku z tym od lat prowadzone są intensywne badania koncentrujące się m.in. na etiologii i przebiegu tego typu schorzeń. Ważnym kierunkiem badań nad patogenezą chorób neurodegeneracyjnych są analizy oceniające ich potencjalny aspekt genetyczny. Wiele badań skupia się także na czynnikach pozagenomowych, podkreślając, że wiele z nich może mieć istotny wpływ na przebieg tych chorób.

Słowa kluczowe: czynniki genetyczne, zaburzenia neurodegeneracyjne, uwarunkowania pozagenomowe

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INTRODUCTION

Advances in science and medicine have led to an extended human lifespan. The elderly population is constantly increasing. This change in demographic structure results in problems of age-related diseases. For a long time, scientists have been observing an increase in the incidence of neurodegenerative diseases, which are characterised by changes in the nerve cells of the central nervous system. Neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, and Huntington's disease, among others. These are incurable diseases characterised by a debilitating effect on the body (Gitler et al., 2017). Their common feature is a pathological process that leads to the loss of nerve cells through apoptosis or necrosis. They contribute to the progressive degeneration and/or death of nerve cells. The result is a reduction in mental performance as well as mobility problems. Despite differences in the course of the diseases and their symptoms, at a molecular level, three main features can be distinguished by which a disease is classified as a neurodegenerative disorder. Firstly, the accumulation of toxic protein aggregates in the cells of the nervous tissue of the brain; secondly, the disturbed function (i.e. dysfunction) of the mitochondria; and thirdly, damage caused by reactive oxygen species, both those supplied from outside and those produced by body cells. The process leading to the development of symptoms of neurodegenerative diseases starts much earlier and the disorders are often asymptomatic for years. The first symptoms appear when a significant number of neurons or a specific part of the central nervous system is damaged. The aim of this study was to present the current state of knowledge on the aetiopathogenesis of neurodegenerative disorders, devoting attention not only to neurophysiological and clinical aspects, but above all to the genetic and extra-genomic mechanisms underlying these conditions (Dugger and Dickson, 2017).

GENETIC FACTORS IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

In 1–5% of cases, Alzheimer's disease is the familial form with a genetic basis that appears relatively early, i.e. under 65 years of age. It is an autosomal dominantly inherited disorder, with various genes playing a role in its aetiology. Mutations in the genes of three proteins: APP (amyloid precursor protein), presenilin 1 (*PSEN 1*), and presenilin 2 (*PSEN 2*) are thought to be the cause. A number of pathogenic mutations have been found in each of these genes, with more than 150 in the *PSEN 1* gene alone. These mutations disrupt, among other things, the production of the Aβ protein, contributing to its aggregation as well as neuronal degeneration (Naj and Schellenberg, 2017). As a consequence of both genetic and non-genetic factors, the metabolism of Aβ protein is impaired in Alzheimer's disease, resulting in the formation of senile plaques and tau protein (Sadigh-Eteghad et al., 2015). The Aβ protein is formed by the breakdown of the APP protein. APP protein is a large protein representing one of the components of the neuronal cell membrane, and has neuroprotective activity (Sosa et al., 2017). Within the APP protein, the 40–42 amino acid sequence of the Aβ protein, or amyloid β protein, is present. APP protein is degraded by two types of proteases: β-secretase and α-secretase (Chen et al., 2017). In the process of normal metabolism, APP is cleaved into soluble fragments by the properly functioning enzyme α-secretase. β-secretase cuts the sequence of the Aβ protein at its first amino acid site, followed by the action of another protease, γ-secretase, which cuts this protein from its other side at the 40–42 amino acid level. This leads to the formation of two isoforms of the Aβ protein, either 40 or 42 amino acids long. In Alzheimer's disease, the level of the 42 amino acid isoform is elevated; it has an increased ability to assemble into complexes of several molecules and then to form Aβ fibres (fibrils), followed by diffuse plaques, and finally mature senile plaques. Studies show that oligomers of the Aβ protein, diffusing in the brain, are toxic and contribute to neuronal atrophy (Pesz et al., 2011).

Importantly, γ-secretase includes presenilin 1 or presenilin 2, i.e. the proteins whose mutated genes are responsible for familial forms of Alzheimer's disease. It has been suggested that *PSEN 1* may act as a cofactor for γ-secretase, or also act as a γ-secretase. Presenilins are genes actively involved in APP proteolysis. Mutations in the presenilin genes are an important cause leading to the formation of 40- and 42-amino acid amyloid β-peptides (Joshi and Wang, 2015). Another factor involved in the cascade of neurodegenerative reactions is the tau protein. Among other mechanisms, it interacts with Apo E (apolipoprotein E) and β-amyloid. In many neurons located in brain regions that are damaged in Alzheimer's disease, there are large, membrane-unbound neurofibrillary tangles. They consist of helically coiled paired filaments. Hyperphosphorylated tau protein is their main component. Excessive phosphorylation of the tau protein causes impairment of microtubule function, disruption of the nerve cell cytoskeleton, loss of axonal transport, and ultimately cell destruction. The presence of amyloid deposits, neurofibrillary tangles and neuronal loss result in the development of dementia and impaired memory function (Ossowska, 2018).

An important genetic factor in the pathogenesis of Alzheimer's disease is Apo E. It is a glycoprotein synthesised locally in astrocytes. It is encoded by a gene located on chromosome 19 and occurs as three isoforms: ε2, ε3 and ε4. It has been shown that the brain is the site of highest mRNA expression of Apo E, and that Apo E synthesis increases in states of neuronal damage in both the peripheral and central nervous systems. The occurrence of the ε4 allele is associated with increased amyloidogenesis. The presence of two copies of the ApoE4 allele increases the risk of Alzheimer's disease 16-fold. In addition, elevated cholesterol concentrations in neuronal cell membranes increase the aggregation

of nascent Aβ, stimulate plaque formation, and induce hyperphosphorylation of the tau protein (Elliott et al., 2010).

GENETIC FACTORS IN THE PATHOGENESIS OF PARKINSON'S DISEASE

The role of genetic factors in the pathogenesis of Parkinson's disease has been the subject of numerous studies. *SNCA* (synuclein alpha) was the first gene to be shown to increase the risk of developing Parkinson's disease. A mutation occurring within this gene, which encodes α-synuclein, was shown to be the cause of the condition (McFarlane and Kędziora-Kornatowska, 2020). Mutations in the gene that encodes the neuronal protein α-synuclein are most likely to increase the risk of developing the spontaneous form of Parkinson's disease, characterised by early onset, and are associated with a variant of the disease inherited in an autosomal dominant manner. As a result of abnormal folding, α-synuclein becomes insoluble and produces aggregates, intracellular fibrillar deposits found within the nerve cell body, Lewy bodies, and nerve protrusions. Other misfolded proteins, such as phosphorylated tau protein or amyloid-β protein, are also part of Lewy bodies. In its physiological state, α-synuclein occurs in the form of unfolded monomers or, when bound to lipids, α-helices. The α-synuclein monomers, once they adopt a β-sheet structure, have the ability to aggregate. Their aggregation results in the formation of oligomers, which subsequently develop into fibrils – the main components of Lewy bodies. Further genes identified include the *PINK1* (PTEN-induced kinase 1) and *Parkin* genes. Mutations in these genes lead to a loss of the ability of proteins to bind harmful mitochondrial breakdown products, the accumulation of toxic components in cells, and oxidative stress (Goedert et al., 2013).

It has been found that approximately 5–10% of patients carry a mutation in the *GBA* gene, which encodes the enzyme glucocerebrosidase. In this situation, the risk of developing Parkinson's disease increases up to 20-fold. Observed alterations in other genes, the presence of which may also correlate with the onset of Parkinson's disease, include genes responsible for the occurrence of hereditary ataxia associated with reduced motor coordination. Genes that encode proteins responsible for reducing the adverse effects of environmental factors on the risk of developing Parkinson's disease have also been investigated (Deas et al., 2011).

OXIDATIVE STRESS

For a long time, it has been thought that the concept of oxidative stress may be important in the aetiology of various neurodegenerative diseases. Oxidative stress is a type of homeostatic disorder characterised by the predominance of oxidative processes over antioxidative processes of cellular metabolic pathways. Reactive oxygen species (ROS) are the cause of this condition. The brain is highly susceptible to oxidative damage, given its high oxygen consumption and high mitochondrial activity, while at the same time there are low levels of enzymes whose task is to remove reactive oxygen species. The generation of reactive oxygen species – ROS – or chemically active molecules takes place during physiological processes (Chen et al., 2012). Excessive amounts of these result in oxidative damage to the basic building blocks of body cells, which include proteins, lipids, or nucleic acids (Lushchak et al., 2021). Excessive production of RFTs (replication focus targeting sequence) is not the only cause of oxidative stress. Reduced activity of antioxidant enzymes and/or reduced levels of reducing factors can also play a role. The condition occurs when pro-oxidant factors generated in the cell are so abundant that defence mechanisms in the form of antioxidant and free radical scavenging enzymes lose their ability to cope with the amount of antioxidants. Because of the significant content of polyunsaturated fatty acids in the neural tissue, the intense oxygen metabolism, and the relatively low activity of antioxidant enzymes, the brain is particularly susceptible to oxidative stress (Van Raamsdonk et al., 2017). The detailed mechanism by which oxidative stress increases in neurodegenerative diseases has not yet been fully uncovered. Many researchers have suggested a link between the deposition of abnormal forms of proteins and the increase in oxidative stress. Numerous studies indicate a link between β-amyloid toxicity and free radical generation in Alzheimer's disease. An increase in protein nitration and oxidation is observed in brain areas with amyloid plaques and neurofibrillary degeneration (Mangialasche et al., 2009). Given the major role of oxidative stress in the pathogenesis of neurodegenerative diseases, studies have been conducted to investigate the effects of antioxidants on the course of these conditions. The properties and mechanism of action of antioxidants bring into question the possibility of their use in the prevention and treatment of Alzheimer's disease (Tamagno et al., 2021). An important antioxidant is glutathione (GSH). Its function is to protect the cell from oxidative stress (Kumar et al., 2015).

In addition to playing an important role in the removal of reactive forms of oxygen, GSH is involved in the regeneration of vitamins C and E (Baek and Lee, 2016). In the course of neurodegenerative diseases, a reduced concentration of glutathione is observed. It has been shown that an increase in the concentration of GSH in cells may result in slowing the development and alleviating the course of these diseases. Glutathione is an organic chemical compound present in small amounts in food. An increase in its concentration under the influence of consumed foods is small but it is a protective function, shielding cells against oxidative stress. Intracellular antioxidants also include coenzyme Q10 (CoQ10). It is an essential compound synthesised in the inner mitochondrial membrane. Its reduced form, which is ubiquinol, has antioxidant properties. Ubiquinol binds RFTs, preventing lipid peroxidation and oxidative damage to proteins and DNA (Winiarska-Mieczan, 2018).

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THE IMPORTANCE OF INTESTINAL MICROBIOTA IN THE PATHOGENESIS OF NEURODEGENERATIVE DISORDERS

Within the human intestines, a distinct ecosystem exists for each individual, shaped by a diverse group of microorganisms. This ecosystem is referred to as the gut microbiota. The microbiota, otherwise the microbiome, is composed of microorganisms of all kinds. Clusters predominantly inhabiting the gastrointestinal tract include *Firmicutes* and *Bacteroidetes* (Grigg and Sonnenberg, 2017). The composition of the microbiota is affected by many factors, including stress, diet, age, genetic factors, or the use of antibiotics during treatment. Communication on the microbiota–gut–brain pathway is bidirectional and can occur via immunological, neuronal, and humoral pathways. The study of these relationships has had a significant impact on studies investigating the role of probiotic strains in diseases of the nervous system. The digestive system is responsible, among others, for transmitting information about the current physiological state; it also receives signals from the central nervous system (CNS) (Carabotti et al., 2015). Currently, more and more studies indicate the existence of a relationship between the composition of the intestinal microbiota and the functioning of the brain. The connection that enables two-way communication is referred to as the intestinal-brain axis (or brain–intestinal microbiota axis). The GBA consists of the CNS, including the brain and spinal cord, the enteric nervous system (ENS), the autonomic nervous system, and the hypothalamic–pituitary–adrenal (HPA) axis (Browning and Travagli, 2014). The main functions of the intestinal–brain axis are the integration of intestinal functions and the connection of emotional and cognitive centres of the brain with peripheral intestinal functions and processes, such as activation of immunity, intestinal reflex, intestinal permeability, and enteroendocrine transmission (Anglin et al., 2015).

There are three known neuronal mechanisms by which signals are transmitted: endocrine, metabolic, and immunological. The nervous pathway works through the intestinal nervous system, mainly the autonomic nerves of the nervous system which control the function of the digestive system and the vagus nerve. This is how sensory information is transmitted from the internal organs to the CNS. The activation of the vagus nerve is necessary for the effective impact of intestinal microbiota and probiotics on the brain (Mayer et al., 2014).

The intestinal microbiota is involved in the regulation of the HPA axis, which plays a role in the body's response to stress. The action of this axis is based on the principle of negative feedback, a key self-regulatory mechanism, the activation of which involves many endocrine steps (Wang and Kasper, 2014).

The hypothalamus produces corticoliberin, which stimulates the production of adrenocorticotropic hormone in the pituitary gland, leading to the formation of cortisol, the end product of the reaction, which is then secreted by the adrenal cortex (Rea et al., 2016). The effect of the intestinal bacterial biota on the functioning of the HPA axis was demonstrated in 2016, in studies on GF mice. The researchers concluded that in the prefrontal cortex of animals bred under sterile conditions (germ-free) there is an increase in the expression of genes encoding transcription factors for myelination pathways, which are involved in the terminal maturation of oligodendrocytes, and an increase in the expression of mRNA of the gene controlling myelination. This leads to an increase in the number of axon myelin plaques, which correlates negatively with the efficiency of nerve signal transmission (Morrison and Preston, 2016).

The body aging process brings with it a gradual weakening of all physiological functions. In the digestive tract of the elderly, there are numerous changes in the composition and functioning of the intestinal microbiota. This can contribute to the development of diseases and cause local as well as systemic inflammation. Deficiencies of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) in the brain and some neurotransmitters, such as 5-HT, have also been reported in the elderly. As a result of these deficiencies, the functioning of neurons is impaired. All of this contributes to an increase in the incidence of neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Szewczyk et al., 2019).

CONCLUSION

The aetiology of numerous neurodegenerative diseases is still not fully understood. Therefore, intensive research has been ongoing for years, focusing, among other aspects, on the cause and course of these conditions. Due to the phenomenon of ageing populations, the proportion of people suffering from dementia syndromes is increasing, and proper diagnosis and therapy of age-related conditions are of vital importance. Early and accurate diagnosis of neurodegenerative diseases is still a challenge for modern medicine, but current research holds promise for further progress in this field. An important direction of research into the pathogenesis of neurodegenerative diseases is assessment of their potential genetic aspects. Many studies also focus on non-genomic factors, highlighting that many of them can have a significant impact on the course of neurogenerative diseases.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study: JB. Collection, recording and/or compilation of data: JB. Writing of manuscript: JB. Critical review of manuscript: ES. Final approval of manuscript: ES.

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