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Neurodegenerative diseases- Characteristics and The role of physical activity

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ABSTRACT

Introduction

Neurodegenerative diseases, increasingly prevalent due to an aging population, involve the degeneration of nerve cells through processes like necrosis and apoptosis. These conditions, such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and Huntington's, affect the brain, spinal cord, and peripheral nerves, leading to motor, psychological, and memory disorders, and can result in premature death. Research indicates that physical activity from a young age can reduce the risk of developing neurodegenerative diseases, with studies showing that exercise induces beneficial neuroplastic changes in both healthy individuals and patients.

Aim of the study

The aim of the study is to provide a comprehensive analysis of neurodegenerative diseases. Through a detailed discussion of these issues, our goal is to increase public awareness of neurodegenerative diseases and provide readers with comprehensive knowledge about this diseases.

Material and method

This article presents the current state of knowledge about neurodegenerative diseases. A literature review was conducted using the PubMed, Google Scholar and Web of Science databases, utilizing keywords such as " Parkinson's disease", " amyotrophic lateral sclerosis", "Alzhaimer's disease".

Keywords

Parkinson's disease, amyotrophic lateral sclerosis, Alzhaimer's disease, dementia

Introduction

In recent years, neurodegenerative diseases have become one of the most common health problems facing humanity. The noticeable increase in their prevalence is closely related to the aging process of society. Neurodegenerative diseases include congenital or acquired disorders of the nervous system, which result in the degeneration of nerve cells. This process can occur through necrosis, characterized by protein denaturation, cell swelling, loss of membrane integrity, cell lysis, and the triggering of an inflammatory response, or through apoptosis, which is the programmed death of the cell.

These diseases can affect various areas of the brain, spinal cord, and peripheral nerves, leading to symptoms related to motor, psychological, and memory disorders, including dementia. This results in the improper functioning of basic bodily functions and can lead to premature death. Neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease[1].

There are many processes that lead to the damage and death of nerve cells, such as oxidative stress, reduced blood flow in the brain, and excitotoxicity[2].

Recent reports indicate that physical activity at a young age reduces the risk of developing neurodegenerative diseases, such as Parkinson's disease. Furthermore, numerous scientific studies conducted on animals and humans show that physical exercise induces beneficial neuroplastic changes in the brain in both healthy individuals and patients with neurodegenerative diseases[3].

Alzheimer's Disease

Alzheimer's Disease (AD) is the most common cause of dementia. The number of affected individuals continues to grow at an increasingly rapid pace. Currently, in Poland, about half a million people are affected, and by 2050, this number could increase fourfold. According to the World Alzheimer Report 2016, worldwide in 2016, 28.5-33.3 million people were affected. AD primarily affects individuals over the age of 50, with an average onset age of 58 years[2,4,5].

The cause of the disease is the accumulation of misfolded β-amyloid protein in the brain. This is a 42-amino acid fragment of a peptide that is a precursor to β-amyloid (βAPP, Beta-Amyloid Precursor Protein). βAPP consists of 700 amino acids and is encoded by a gene located on the long arm of chromosome 21. It is a component of neuronal cell membranes and participates in axonal transport, with presumed neuroprotective abilities. Its proper breakdown into soluble fragments is facilitated by the enzyme α-secretase. If fragmentation occurs due to the action of γ-secretase and then β-secretase, pathological, insoluble forms of β-amyloid, namely Aβ40 and Aβ42, are formed. These accumulate intra- and extracellularly as amyloid plaques. Their presence causes neuron death through hyperphosphorylation of tau protein (microtubule-associated protein tau) by enzymes, especially GSK 3β (glycogen synthase kinase 3 beta). Abnormal tau protein becomes a component of neurofibrillary tangles (*NFTs*), intracellular protein aggregates in the cytoplasm of nerve cells. This leads to impaired metabolism, disrupted intracellular transport, neuron degradation, damage to neuronal connections, and a decrease in neurotransmitters, with acetylcholine being crucial for memory

processes. Amyloid aggregates also deposit in the walls of brain capillaries, reducing blood flow [2,6,7].

The etiology of Alzheimer's Disease depends on genetic and environmental factors. About 10-20% of cases are inherited in an autosomal dominant manner. The early onset of the disease, occurring in patients below 65 years of age, is associated with mutations in the APP (amyloid precursor protein – coding for β-amyloid precursor protein), PSEN1 (Presenilin-1 – coding for presenilin 1), and PSEN2 (Presenilin-2 – coding for presenilin 2) genes. Very early onset AD, manifesting as early as 40 years of age, occurs in individuals with trisomy 21. A significant role in the development of the late form of the disease is played by the ε4 variant of the apolipoprotein E gene (19q13.2), which increases susceptibility to the disease threefold in heterozygotes and fifteenfold in homozygotes. The remaining 80-90% of cases have various etiological factors[2,7,8].

Initial symptoms of Alzheimer's Disease are often mistaken for stress or age-related changes. The earliest symptoms include short-term memory disturbances. The patient forgets recent events, has difficulty assimilating new information, and forgets basic words while recalling distant past events well. In the later stages, long-term and procedural memory, as well as time and space orientation, are affected. The patient may not know where they live, who they are, fail to recognize close family members, or even their own reflection in the mirror. There are also concentration disturbances and behavioral changes such as anxiety, irritability, and aggression. Hallucinations, particularly visual, mood disturbances like depression, psychomotor agitation, and sleep problems are common. In advanced stages, seizures and other neurological symptoms may occur [2].

To diagnose the disease, in addition to subjective and physical examinations, basic laboratory tests are necessary to rule out other causes of cognitive impairment. Neuropsychological and neuroimaging tests such as computed tomography and magnetic resonance imaging of the brain are conducted (they do not confirm the disease but can reveal the characteristic reduction in hippocampal volume and medial temporal lobe atrophy associated with Alzheimer's). Positron emission tomography is also used to image β-amyloid deposits, and cerebrospinal fluid examination is performed to determine tau protein levels [6,7].

Parkinson's disease

Parkinson's disease (PD) is a heterogeneous disorder first described by Dr. James Parkinson in 1817, who called it the "shaking palsy." It primarily affects individuals between the ages of 50 and 60, although it can appear before the age of 40. The risk of developing the disease increases with age and is higher in men. The exact pathogenesis is not fully understood [9,10].

The disease is associated with neurodegeneration in the substantia nigra, leading to dopamine deficiency in the striatum and an excess of glutamatergic neuron transmission, which inhibits the thalamic nuclei. Both genetic and environmental factors, including oxidative stress and free radicals, contribute to the disease's pathogenesis. The substantia nigra contains dopamine, neuromelanin, and shows high monoamine oxidase activity, making it particularly susceptible to oxidative stress[10,11].

In brain regions affected by the pathological process, Lewy bodies are observed in the cytoplasm of neurons. These are abnormal, eosinophilic protein aggregates primarily composed of α-synuclein (AS), whose presence leads to neuronal cell death via apoptosis. There is a clear link between point mutations in the AS gene and the genetic predisposition to the disease. However, this is a rare case of PD. Much more frequently, in over 85% of patients, the disease develops spontaneously [4].

The death of cells in the pars compacta of the substantia nigra, where dopaminergic neurons are located, leads to a decrease in dopamine levels in the brain. Dopamine plays a key role in controlling movements, muscle tone, and coordination.

The primary symptoms of Parkinson's disease include bradykinesia (slowness of movement), resting tremor with a frequency of 4-6 Hz (involuntary movements of certain body parts caused by contractions of antagonist muscles, mainly affecting the upper limbs and head), postural instability, increased muscle tone of a plastic type, and the characteristic "masked face" [9].

Preclinical symptoms preceding the disease may include depression, constipation, olfactory disturbances, and limb paresthesia. These can precede the onset of the disease by up to 10 years. Other clinical symptoms include autonomic disturbances such as drooling, seborrhea, and sweating. Additionally, there may be unclear speech, infrequent blinking, and changes in handwriting due to tremors and muscle rigidity in the hands, which patients particularly notice [2,12,15].

The course of the disease is usually slow and progressive. PD symptoms are associated with a deep dopamine deficiency in the striatum, so treatment aims to increase the level of this neurotransmitter. This includes stimulating the dopaminergic system, increasing endogenous

dopamine production, or using monoamine oxidase (MAO) inhibitors and catechol-O-methyltransferase (COMT) inhibitors – enzymes that break down dopamine. The precursor to dopamine is L-DOPA (levodopa, LD), which, unlike dopamine, can cross the blood-brain barrier and is the primary and most effective drug used in treating this disease. The conversion of levodopa to dopamine via aromatic L-amino acid decarboxylase occurs in the central nervous system, increasing the concentration of this neurotransmitter in the brain. This process can also occur in peripheral tissues, causing various side effects and reducing the availability of this precursor for nerve cells, so it is usually used with peripheral aromatic amino acid decarboxylase inhibitors such as carbidopa or benserazide. Initiating Parkinson's disease treatment with levodopa brings immediate improvement. It has a very short half-life (90-120 minutes), causing significant fluctuations in the amount of produced dopamine, so it is administered several times a day. This is particularly important for patients with advanced disease, as their motor state, with a deep deficiency of endogenous dopamine, depends on taking the medication. Unfortunately, after 3-5 years of use, about 50% of patients develop undesirable symptoms such as motor fluctuations (variations in motor state from periods of normal functioning (patient is "on") to periods of "off" when there are movement difficulties), choreic dyskinesias (resulting from peak dose), dystonic dyskinesias (due to decreased LD levels), and biphasic dyskinesias. Levodopa may also cause sleep disturbances, psychotic symptoms (usually visual hallucinations, delusions), and orthostatic hypotension [2,12,13]..

Another therapeutic option is the use of dopaminergic receptor agonists – ropinirole, rotigotine, pramipexole- the second most potent group of drugs. These are recommended in monotherapy for younger patients in the early stages of the disease, leading to a much later onset of dyskinesias and fluctuations than in patients treated with LD from the start. They can also supplement levodopa therapy in patients with motor complications.

In Parkinson's disease, entacapone- a COMT inhibitor and selegiline and rasagiline- MAO-B inhibitors are also used, improving the quality of life for patients treated with L-DOPA and reducing the body's need for the drug [12,14,16].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is an incurable, progressive neurodegenerative disease of unknown etiology and pathogenesis, leading to damage of both upper and lower motor neurons. ALS is also known as "Charcot's disease," named after the eminent French physician Jean Martin Charcot, who first described it, and "Lou Gehrig's disease," popular

primarily in the United States, named after the renowned American baseball player Henry Louis Gehrig, who died from the disease in 1941 [4,17].

The disease can occur at any age, but symptoms most commonly appear between the ages of 55 and 75, affecting men more frequently than women. Most patients die within 3 to 5 years from the onset of symptoms due to respiratory failure. Only 5% of patients survive 10 or more years [18].

Amyotrophic lateral sclerosis can be categorized into two main forms: sporadic (Charcot's disease, accounting for up to 90% of cases) and familial (FALS, comprising 5-10% of cases) [19].

Genetically predisposed forms of ALS typically manifest at an earlier age than sporadic forms and are usually inherited in an autosomal dominant pattern. A mutation in the gene on the long arm of chromosome 21 at position 22 (21q22), encoding superoxide dismutase 1 (SOD1), occurs in 20-30% of patients and contributes to oxidative stress reactions [20].

Other genes whose mutations can lead to ALS include NAIP, EAAT2, VEGF, angiogenin, peripherin, SPG4, and dynactin.

Typical initial symptoms of ALS include weakness and atrophy of the short muscles of the hands, followed by the shoulder girdle and progressive spastic paralysis of the lower limbs, along with weight loss ("limb onset").

In 25% of cases, bulbar symptoms ("bulbar onset") such as speech, swallowing, and drooling disorders are the initial symptoms. A rare form affecting 1-2% of patients is the "respiratory onset," where symptoms begin with breathing difficulties due to weakened intercostal muscles.

As the disease progresses, further muscle groups atrophy, motor function deteriorates, bulbar symptoms worsen, bilateral positive Babinski reflex appears, and in later stages, paralysis and flexor contractures develop.

Typically, ALS does not present with sphincter disorders, sensory disturbances, dementia, eye movement disorders, or bedsores.

Amyotrophic lateral sclerosis gradually impairs physical function but not intellectual capacity. Individuals affected by this disease maintain awareness and intellectual abilities throughout their lives, often leading to anxiety, depression, sleep disturbances, and mood swings. The most common cause of death is respiratory failure due to paralysis of the respiratory muscles and pulmonary complications. As of now, there is no effective treatment for ALS. The only available and recommended drug is Riluzole, which does not significantly

impact quality of life or disease progression but may slightly extend life by an average of 2-4 months.

Treatment options also include psychotherapy, physical rehabilitation, and palliative care, which help alleviate symptoms, address nutritional issues, and provide psychological support [21,22,23].

The role of physical activity in neuodegenerative diseases

Regular physical activity is recognized as crucial in the context of neurodegenerative diseases, as it aids in lowering the risk of these conditions and slows their progression. Despite this, the exact molecular mechanisms involved are not yet completely understood. Neurotrophins, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glia cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4), have been identified as significant contributors to brain health, given their roles in neurogenesis, neuronal survival, and synaptic plasticity. Physical exercise has been shown to increase the production of these neurotrophic factors, which are typically reduced in neurodegenerative diseases, indicating their essential role in brain health maintenance. However, the precise mechanism by which exercise enhances neurotrophin production is still unclear, which limits their potential application in developing therapeutic strategies for treating neurodegenerative diseases [24,25].

Physical exercise is known to enhance various health conditions, support brain health, and maintain cognitive function. Numerous studies have shown that aerobic exercise, in particular, positively affects synaptic plasticity, significantly improving neuroplasticity related to learning, memory, and motor function. The benefits of physical activity are especially notable in the context of neurodegenerative diseases, as exercise helps slow the progression of disorders that affect the nervous system and lowers the risk of their development. This prevention of cognitive and physical decline, common in age-related diseases, is likely due to the reduction of neurotoxic amyloid aggregates, oxidative stress, neuroinflammation, and neuronal death [24,25].

The key mediators of this beneficial effect have been neutrophins because of effect due to their ability to promote neuronal survival, development, maintenance, neurogenesis, and synaptic plasticity. Physical exercise is known to increase the expression of neurotrophins through mechanisms that may involve the production of specific metabolites and/or the activation of enzymes involved in epigenetic modifications regulating gene transcription. However, the underlying mechanisms are not yet fully understood, limiting the use of neurotrophic factors in developing potential therapeutic strategies. Notably, neurotrophins may

exert their beneficial effects on brain health and motor function through a synergistic action that can be maximized by physical exercise. It is well known that skeletal muscle acts as an endocrine organ capable of secreting various neurotrophic factors with beneficial and neuroprotective effects. Therefore, it is essential to investigate the mechanisms by which neurotrophic factors released by both the brain and skeletal muscle in response to exercise could act synergistically to ensure brain health and counteract the cognitive decline associated with neurodegenerative diseases [24,25,26].

Conclusions

In recent years, the age structure of the human population has been undergoing significant changes. An increasing number of individuals are reaching old age, leading to a significant rise in patients diagnosed with neurodegenerative diseases. Despite considerable advances in medicine, an appropriate causal treatment regimen for these diseases has not yet been developed.

The disease process in neurodegeneration can begin long before the appearance of initial symptoms. Unfortunately, these changes can persist for many years without clear symptoms. The first noticeable changes in functioning only arise when a significant number of neurons in the brain or a specific part of the central nervous system are damaged.

Regular physical activity is essential in lowering the risk and slowing the progression of neurodegenerative diseases, though the exact molecular mechanisms are not fully understood. Neurotrophins like BDNF, NGF, GDNF, NT-3, and NT-4, which support neurogenesis, neuronal survival, and synaptic plasticity, are increased through exercise, highlighting their importance in brain health maintenance.

Author`s constribution

Conceptalization, Magda Madoń and Daria Sieniawska, methodology, Daria Sieniawska and Julia Sieniawska, software, Daria Sieniawska, Angelika Kamizela, check Magda Madoń and Julia Sieniawska, formal analysis, Magda Madoń and Julia Sieniawska, investigation Daria Sieniawska, resources, Julia Sieniawska, Angelika Kamizela, data curation, Magda Madoń, writing-rough preparation, Magda Madoń, Daria Sieniawska, Julia Sieniawska, visualization, Magda Madoń, supervision, Julia Sieniawska, project administration, Magda Madoń, Daria Sieniawska, Angelika Kamizela and Julia Sieniawska. All authors have read and agreed with the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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