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Overview of neurodegenerative disease

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Abstract

Neurodegenerative diseases are connected with the degeneration of neurons, together with they may be of genetic origin or develop due to environmental factors. These diseases affect certain features of neurons and result in the inability to fully fulfill or lose some functions in the person. The leading neurodegenerative diseases are Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) disease. The epidemiology and pathogenesis of these and other neurodegenerative diseases have not yet been completely explained. Within the scope of this research, neurodegenerative diseases are closely examined, the treatments applied are evaluated, and the molecular changes in the formation and course of the disease are detailed.

1. Introduction

The term neurodegeneration is formed by the combination of the word's neuron meaning nerve cell and degeneration meaning loss of function [1].

Neurodegenerative diseases include the group of diseases that result in death, the mechanism of formation has not yet been fully elucidated and there is no definitive treatment. One of the main reasons why these diseases cannot be treated is that neurons lack the ability to divide or have very little ability to divide. However, recent studies show that it is possible to treat neurodegenerative diseases with stem cells [1].

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. This is followed by Parkinson's disease (PH) and amyotrophic lateral sclerosis (ALS), Huntington's disease, frontotemporal dementia, spinocerebellar ataxias, spinal muscular atrophy (SMA). As a result of these diseases, abnormal symptoms such as cognitive disorders, limitations in mobility, difficulties in speaking, breathing difficulties, memory loss are observed [1].

Basic molecular changes in the formation of neurodegenerative diseases; It includes many molecular changes such as regression and positive aggregation, accumulation of specific proteins in the cell, protein abnormalities in the cell, anatomical fragility of the 3D structure of proteins, neuronal abnormalities, apoptosis mechanism characterized as programmed cell death, inflammation, intracellular oxidative and proteomic stress. In addition to these, among the factors that increase the risk of developing neurodegenerative disease, hormone levels, caffeine-containing food use, infection status, age and gender are also counted. Especially with the increase in age, the risk of developing neurodegenerative diseases increases as well. However, the vast majority of these diseases are known by postmortem autopsy [1].

The basis of the grouping of neurodegenerative diseases under the common disease group is to consider the diseases mentioned one by one and to examine the formation processes of these diseases in determining their

pathogenesis. These diseases are grouped and named as neurodegenerative diseases, with the findings of genetic and molecular changes between diseases meeting at a certain point [2].

Studies on the treatment of neurodegenerative diseases, which have become more common in the last 40 years due to the increase in age in human populations, have gained momentum with modeling. The models used can be 3D as well as animal models. With the animal models created, it is aimed to illuminate the multifaceted structure of neurodegenerative disease or diseases. The created animal models simulate the nature of the disease. Transgenic mice are the most commonly used animal models [1].

Apart from modelling, treatment methods in neurodegenerative diseases are researched and developed with genome sequencing techniques and next generation sequencing technologies [1].

2. Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease that causes neuromediator dysfunction affecting the central nervous system, peripheral nervous system and enteric nervous system. Parkinson's disease, which is known as movement disorder, is one of the slow progressing neurodegenerative diseases, which is generally seen in advanced ages. Until the disease is diagnosed, neuronal losses have greatly increased [3-4].

The etiology of the disease is not yet fully known. However, there are factors that increase the risk of Parkinson's disease [3-4].

2.1. Epidemiology of Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disease that occurs in middle and advanced ages, progresses progressively and spreads over long periods such as 10-20 years [5]. It affects 1%-2% of people over the age of 65 and 4% of people over the age of 80. The incidence is higher in men than in women [5]. It is known that Europeans are more affected by Parkinson's disease than Asians [5].

2.2. Pathophysiology of Parkinson's disease

Parkinson's disease is associated with the accumulation of α-synuclein proteins in cytoplasmic inclusions called Lewy bodies in neurons and the loss of dopaminergic neurons and the loss of these losses in the substantia nigra from the basal ganglia [6].

The accumulation of α-synucleins in the Lewy body is widespread in the neocortical and cortical regions of the brain. Lewy bodies formed by the accumulation of α-synucleins damage the connections between neurons and stop neuronal transmission and neurotransmitter secretion [6-7].

It develops due to neuronal losses of substantia nigra pars compacta (Snpc) cells in the brain stem that secrete dopamine. Dopamine is a neurotransmitter chemical and is involved in many important events that occur in the brain, such as metabolic activities, physiological movements, and neuronal transmission. The SNPC region of the brain contains approximately 800,000 cells, and approximately 60%-80% of these cells must be lost for a diagnosis of Parkinson's disease [8]. The rate of disease seen from the mentioned genetic and molecular factors is around 5% - 10%.

Mitochondrial dysfunction and increased oxidative stress due to increased mitochondrial dysfunction are also involved in the pathosiology of Parkinson's disease. The increase in oxidative stress in the cell results in neuronal losses and is associated with Parkinson's disease. In addition, the ubiquitin-proteosomal system is also involved in the development of Parkinson's disease. As a result of all these molecular changes, misfolded proteins accumulate and pave the way for Parkinson's disease [9].

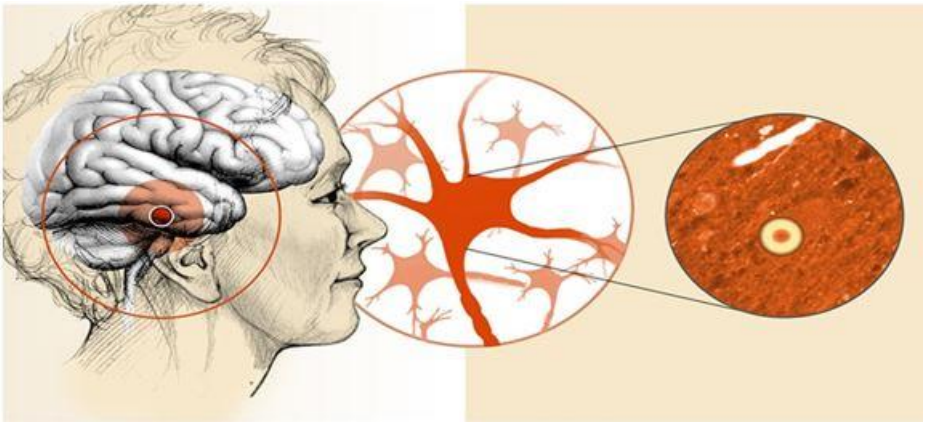

Figure 1. Close-up imaging of Lewy body accumulation in cytoplasmic inclusions in neurons

2.3. Clinical manifestations of Parkinson's disease

Depending on the pathophysiological findings associated with Parkinson's disease, stiffness in the joints, also called rigid limb, due to neuronal losses and lack of transmission between neurons, muscle tremors called resting tremor, muscle spasms called dyskinesia, slowed movements called bradykinesia, decreased voluntary movements called akinesia, It has many clinical symptoms such as difficulty in standing upright, posture disorder, excessive salivation called salivation, difficulty in swallowing called dysphagia, slowing of bowel movements called constipation and consequent constipation, inability to smell, depression, anxiety, sleep fragmentation [10].

2.4. Treatment of Parkinson's disease

There is no cure for Parkinson's disease yet, and existing treatments reduce the patient's symptoms. Medications used for treatment contain the active substance dopamine. In the drug treatment administered to the patient, the response to the active substance is measured [10].

2.5 Genes responsible for Parkinson's disease

Among the genes responsible for Parkinson's disease, PINK1, DJ-1, PRKN, SNCA, PLA2G6, ATP13A2 and FBOX7 are counted [11].

PINK1: This gene is also known as PARK 6. It is an exonic gene encoding protein kinase. It has mitochondrial activity and serine-kinase activity. Its effect in Parkinson's disease has been associated with causing mitochondrial activity disorder. It is the second most common gene mutation in the formation of early Parkinson's disease. These mutations include missense or nonsense mutations. The missense and nonsense mutations it creates are defined and named as p.Gln129fsX157, p.Pro196Leu, p.Gly309Asp, pTrp437X, p.Gly440Glu, p.Gln456X [11].

DJ-1: This gene is also called PARK 7 and consists of 7 exons. It constitutes 1% to 2% of early Parkinson's disease. It is responsible for performing neuroprotective functions and antioxidant functions. As a result of the mutation of the DJ-1 gene, the protein forms conformational changes and goes into misfolding and degradation in the proteomic way. As a result, neuroprotective and antioxidant functions are lost and Parkinson's disease occurs [11].

PRKN: This gene is also called PARK2. It is the second largest gene found in the human genome. It expresses the parkin protein, which is 465 amino acids long. It is broad-spectrum, covering a large number of mutations. There are 887 parkin mutations identified. As a result of mutations in this gene and loss of protein function, neurons become vulnerable to cytotoxic effects, and Parkinson's disease occurs in this case [11].

LRRK2: This gene constitutes the most common mutations in the autosomal inherited form of Parkinson's disease. 50 different mutations are known. It is associated with the formation of Lewy bodies and neuronal losses with the mutations it creates [11].
SNCA: This gene is responsible for the expression of α-synuclein proteins. Lewy bodies and brain pathologies are seen as a result of mutations in this gene [11].

2.5. Environmental risk factors for Parkinson's disease

In the formation of Parkinson's disease, environmental factors as well as genetic factors have an effect on the formation of the disease. Pesticides used as pesticides are at the forefront of these factors. Pesticides are pesticides that are frequently used to combat weeds in agricultural areas. It has been observed that the risk of developing late-onset Parkinson's disease increases in people who use paraquat and maneb derivatives and their ingredients in the pesticide group used in agricultural areas [12].

Another environmental factor that increases the risk of developing the disease is the oxidative stress that occurs after exposure to heavy metals. Oxidative stress occurs as a result of the accumulation of heavy metals in the substantia nigra. This accumulation paves the way for Parkinson's disease. For example; It is known that lead, one of the heavy metals, negatively affects the release of the neurotransmitter dopamine. It causes an increase in lipid peroxidation, decreases antioxidant cell capacity, and as a result causes a-synuclein accumulation [13].

Another heavy metal is lead. It has been observed that the risk of developing Parkinson's disease is doubled by examining the bone structure after exposure to lead [13].

Another heavy metal is manganese. Although manganese does not act as directly as other heavy metals, it is effective in the formation of Parkinson's disease and the accumulation of α-synucleins. As a result of this accumulation, in addition to the symptoms of Parkinson's disease, patients have symptoms called manganism and seen after long-term exposure to manganese [13].

In addition to heavy metals, the concentration of iron ions in the brain should not be above or below certain levels, and the balance should be maintained. While iron deficiency causes disruption in motor functions, iron accumulation due to iron excess forms the basis of neurological disorders [13].

It is known that there are environmental factors that increase the risk of Parkinson's disease, as well as effects that reduce the disease. Among the mitigating effects are the use of cigarettes, alcohol or coffee. The nicotine substance in cigarettes is a neuroprotective substance on its own. It has been observed that nicotine, which is a neuroprotective substance, prevents dopaminergic neuronal toxicity by reducing it [14-15].

3. Amyotrophic Lateral Sclerosis (ALS) Disease

Amyotrophic lateral sclerosis is a progressive fatal neurodegenerative motor neuron disease associated with the degeneration of neurons in the brain and spinal cord. Looking at the name of the disease, the word amyotrophic means lack of muscle nutrition and characterizes the result of atrophy [16-17].

It results in the loss of neurons in the central nervous system, spinal cord, and brain stem. If the motor neurons damaged in ALS disease are composed of upper corticospinal motor neurons, they cause uncontrolled movements called muscle spasticity. If the damaged motor neurons are composed of lower motor neurons, it causes muscle weakness. As a result of the loss of these neurons, various symptoms such as weakness in the legs and muscles, muscle wasting, and swallowing dysfunction are observed. In the last stage of the disease, patients cannot have voluntary muscle movements, so there are cases of paralysis. In addition to these, up to 10% of patients develop dementia in addition to ALS. However, the dementia that occurs is not effective enough to cause the patient to lose cognitive functions [16-17].

None of the studies within the scope of the treatment of ALS disease are in the direction of prevention of the disease, but in the direction of reducing the symptoms of the disease. Drug treatments in use have antiglutamate properties. In addition, one of the treatments used is stem cell therapy. However, successful results of stem cell treatments applied and used have not been recorded [18].

3.1. The pathogenesis of ALS disease

A mutation in the gene encoding the antioxidant enzyme superoxide dismutase 1 (SOD1) plays a role in the pathogenesis of ALS disease. The mutated SOD1 causes conformational change in the enzyme, resulting in misfolding. In addition, ALS disease occurs as a result of incorrect or incomplete activity of the mitochondria organelle. As a result of changes in the structure of motor neurons, axonal or neuronal disruptions, free radical formation, glutamate excitotoxicity, and oxidative stress play an active role in the pathogenesis of ALS disease. [16-17].

3.2. Factors that cause ALS

As with other neurodegenerative factors, environmental and genetic factors play a role in the development of ALS. Environmental factors include many factors such as age, gender, exposure to electrical fields, pesticides, fertilizers, insecticides, formaldehydes, air pollution, alcohol use, smoking and exposure to heavy metals. Genetic factors that are effective in the development of ALS include factors such as familial gene mutations, viral infections, autoimmunity-induced reactions and glutamate excitotoxicity. Only 10% of ALS patients are inherited familial and genetically, while the remaining 90% develop sporadically. The age of onset of the disease varies between 50 and 75 [19].

3.3. Use of models in ALS disease

Models are used to understand the pathogenesis of ALS disease and the expression levels of proteins and genes involved in its pathogenesis, and to identify mutations that play a role in the formation of the disease. Although these models do not fully represent the disease in the human body, they are used in the development of new treatments, uncovering and examining unknown aspects of the disease. Models used in ALS disease can be animal models as well as cell models [20].

3.4. Cell models in ALS disease

It is used to determine the proteins that accumulate and aggregate during the mutation process of the motor neuron with the mutated SOD1 gene by cell models and to examine the toxic effects of these proteins. In the light of cell models, it is aimed to develop methods to treat the disease, including the methods of isolating toxic proteins from cells [20].

In addition, it is a model of applying the desired changes in the genetic structure of the cells taken from the ALS patient with stem cell models and creating induced pluripotent stem cells (IPSC) transplanted to the patient. The created IPSC models are used to predict the therapeutic effects of drugs to be administered as drug therapy in cells. One of the main reasons for the widespread use of this modeling is to transform the skin or blood cells of the person into induced pluripotent stem cells as therapeutic cells [20].

3.5. Worm (nematode) model in ALS disease

C. elegans, one of the worm species that does not have a complex structure, can reach 1 mm in adulthood and has 959 cells, is used. It has been observed that this species preserves its genes by preserving it much better than humans. Since they have a 3-week lifespan and 3-day life cycle, and their 302 neurons have been mapped, they allow healthy monitoring of motor neuron development and imaging under the microscope with fluorescent markers [20].

3.6. Fruit fly (drosophila) model in ALS disease

The fruit fly is very similar to the worm models used in ALS disease. It is preferred because of the presence of fly species with SOD1 gene mutation that causes ALS disease and the phenotypic characteristics of these fly species as a result of ALS disease. It enables the development of drug treatments that are thought to be effective after the phenotypic characteristics of fruit flies with ALS disease, which are described as rough eyes, are observed [20].

3.7. Zebrafish (danio rerio) model in ALS disease

It is preferred because the structure of motor neurons in zebrafish is similar to that of human motor neurons, as in the fruit fly. Zebrafish are a type of fish that can be easily grown in a laboratory environment and reproduce quickly. Likewise, the ability of zebrafish to insert the SOD1 gene, which is the most prominent gene mutation of ALS disease, has made its use in modeling more convenient [20].

3.8. Rodent (mouse) model of ALS disease

The most commonly used animal in the modeling of ALS disease is the mouse, the rodent species. It is used as an animal model thanks to its features such as having motor neurons similar to human motor neurons, having the SOD1 gene mutation, which is the ALS disease gene, having a suitable size for stem cell and gene therapy studies, rapid reproduction and easy breeding. At the same time, rodent-like creatures have a more complex nervous system compared to other living things, allowing for the testing of treatment methods to be developed [20].

3.9. Imaging Methods of Neurodegenerative Diseases

Brain imaging technologies are the leading biomarkers used in neurodegenerative diseases, which are used to diagnose neuronal activity or damage in the brain. These imaging techniques consist of different methods such as magnetic resonance (MRI), computed tomography (CT), functional magnetic resonance (fMRI), positron emission tomography (PET) and single positron emission computed tomography (SPECT). These imaging methods can be used in the diagnosis phase as well as in the follow-up of the course of the disease. In this way, neuroimaging methods have reproducibility [21].

4. Biomarker Use in Neurodegenerative Diseases

As a biomarker or biomarker can measure the biological processes that occur normally in people, it is a feature that includes pathogenic processes, biological processes that occur as a result of the person's encounter with the therapeutic agent and is accepted as the result of the responses of these processes. It is also accepted as an indicator of the biological process in which the symptoms of the suspected disease and the consequences of these symptoms are associated. The use of biomarkers in neurodegenerative diseases provides an opportunity for early diagnosis. It is used not only with the opportunity to make an early diagnosis, but also to determine and monitor the progression of the disease, and to determine the effectiveness of the treatments used as therapeutic agents.

There are some characteristics that an ideal biomarker should have. These features are;

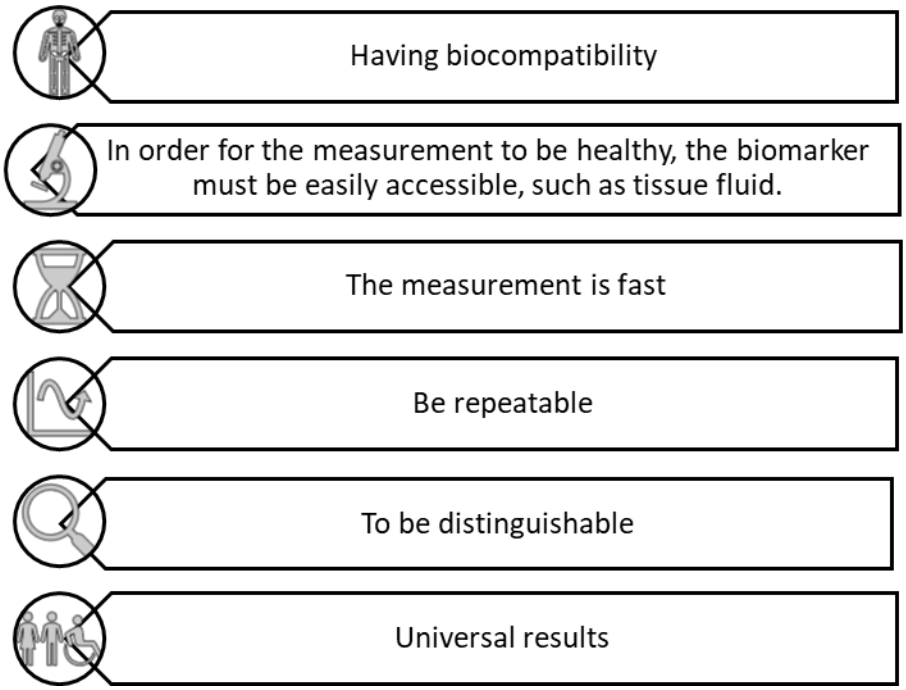

Figure 2. Characteristics of ideal biomarkers

5. Conclusion

Due to the lack of use of biomarkers, it becomes difficult to diagnose the asymptomatic period, which is called the period before the emergence of the disease in the individual. In addition, obstacles such as the widespread use of animal models and the high cost of experiments with animal models are among the factors that make it difficult to develop treatment methods for neurodegenerative diseases. In order to prevent these situations, the use of biomarkers and animal models should be expanded [21].

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Author contributions:

Havva Türkben: Conceptualized, wrote, reviewed**. Furkan Ayaz:** Edited the final version

Conflicts of interest

The authors declare no conflicts of interest.

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