Journal of Experimental and Basic Medical Sciences 2022;3(1):47-53

Review

Diagnostic and Therapeutic Biomarkers for Neurodegeneration

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ABSTRACT

Neurodegeneration is now thought to be an irreversible condition. It is important to have a thorough understanding of these disorders and to take measures and cures if possible before the condition develops. Biomarkers play a critical role in various symptoms. Understanding the mechanisms of diseases can help develop novel biomarkers, which is a crucial step in managing neurodegenerative disorders. This review examined the pathophysiology of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's, disease, and amyotrophic lateral sclerosis, as well as the biomarkers used to diagnose them.

Keywords: Amyotrophic lateral sclerosis, Alzheimer's disease, biomarkers, neurodegeneration, Parkinson's disease, Huntington's disease

Neurons make up the majority of our brains. They are very sensitive cells so any damage, such as a simple blow to the head, may cause their death or some changes in their functions and structure. These functional changes or neuron deaths are called "neurodegeneration" and neurodegeneration may lead to "neurodegenerative disorders" like Alzheimer's disease (AD) and Parkinson's disease (PD). Unfortunately, most neurons cannot divide and their self-repair ability is not as high as other cells such as skin cells. For instance, neurons cannot repair their axons, because of some environmental factors, when they take damage.[1] Therefore it is not easy to deal with these diseases. On the other hand, there are some biomarkers used in the diagnosis of these diseases. Biomarkers are some molecular and chemical methods used to diagnose the disease, determine the treatment method, and watch the treatment's progress.[2]

Biomarkers focus on the pathology of the disease to make a definitive diagnosis besides neuropsychological tests. Using biomarkers provides a more accurate diagnosis and definition of preclinical patients who do not show cognitive impairments such as dementia but develop the pathology of the disease such as plaque formation and accumulation of misfolded proteins in the brain.[3-5]

This may lead to early diagnosis and the necessary interventions for the controlled and positive progression of the disease. This shows the importance of biomarkers.

NEURODEGENERATION

Neurodegeneration is formed by neurodegeneration. Neuro refers to nerve cells and degeneration refers to functional disorders and cell deaths, so neurodegeneration means disorders and cell deaths that occur on neurons. Neurons are responsible for memory and cognitive abilities such as making decisions. Therefore any damage which occurs to neurons affects memory and cognitive abilities directly. The diseases that are caused by neurodegeneration are named neurodegenerative disorders. Although there are numerous neurodegenerative disorders, Alzheimer's disease, Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are the most well-known. All of these diseases are caused by brain damage and neurodegeneration. Neurodegenerative

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Cite this article as: Harmanşa YK, Erbaş O. Diagnostic and Therapeutic Biomarkers for Neurodegeneration. JEB Med Sci 2022;3(1):47-53.

doi: 10.5606/jebms.2022.1008

Received : February 21, 2022
Accepted : February 25, 2022
Published online : June 13, 2022

disorders are similar on cellular levels, although they show different clinical features.[6,7]

Neurons cannot cure themselves against neurodegeneration because they are weak at self-renewal and they cannot divide.[8] Certain cure methods can only slow the progression of the diseases. According to the World Health Organization, neurodegenerative disorders that affect motor function will be the second most common cause of death. Therefore, new therapies for these disorders are required.[9] There is no certain reason for neurodegeneration. On the other hand, it is caused by genetic mutation at a low rate. Other reasons are misfolding protein and a loss of mitochondrial function, leading to the creation of neurotoxic molecules.[7]

ALZHEIMER'S DISEASE

Alzheimer's disease occurs as a result of neuron death and a loss of synapses in the cerebral cortex.[10,11] Some early symptoms may be seen such as dementia, language difficulties or depression, and hallucination. Age has an important role in AD risk factors and the cases, which are observed in people who are under 65 years old, are named early-onset Alzheimer's disease (EOAD), and the other cases, which are observed in people over 65 years old, are named late-onset Alzheimer's disease (LOAD).[12]

Unfortunately, the exact cause of the disease is currently unknown.[13] Besides, it is considered that the disease occurs as a result of an extracellular accumulation of a large amount of β-amyloid as amyloid plaques and intracellular accumulation of neurofibrils.[14] Some hypotheses explain what causes these accumulations. One of them is about genetics. About 1-2% of AD cases are inherited.[15] Any specific gene that affects LOAD has not been determined yet. On the other hand, it is considered that AD risk increases in people who have a variant of the apolipoprotein E (APOE) gene on chromosome 19. Actually, this gene is responsible for producing a protein that carries cholesterol and other fats in the bloodstream. The APOE gene has three different forms. Only one of them increases the risk for AD. Nevertheless, every person that carries this gene is not an AD patient or every person who suffers from AD does not carry this gene, even so, the APOE gene is considered a risk factor. This gene is only a risk-increasing factor.[16]

Another hypothesis concerns β-amyloid. β-amyloid is a piece of amyloid precursor protein (APP). It is known how APP works even though its exact function is not known. Amyloid precursor protein molecules get out of the cell by crossing the cell membrane. In this way, APP breaks into small pieces by other proteins. Some of these pieces stay inside the cell and some of them stay outside the cell. One of these pieces is β-amyloid. This molecule accumulates as amyloid plaques and damages the structures that provide communication between cells. This leads to the fact that immune cells are activated and immune cells cause inflammation. And this results in the death of brain cells.[17,18]

Alzheimer's disease occurs with neuron death. In later stages of the disease, massive loss of brain mass is seen, resulting in atrophy. Degeneration is observed, especially in the temporal lobe and parietal lobe. Also, it can be seen in locus coeruleus which is in the pons.[19] And as a result of this, some dysfunctions may occur in the brain. Finally, it may result in the patient's death at the end periods of the disease.[11,20]

Some methods are used to diagnose AD. The most important and frequently used biomarkers are magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF) tests, and blood tests. It is reported that AD appears with atrophy, and MRI is used to determine atrophy. Atrophy occurs before symptoms appear. In this way, the disease may be diagnosed before it progresses and shows symptoms such as dementia. Also, MRI provides to get information at the microscopic level about neurons and synapse loss.[21,22]

Another brain imaging method is PET. In PET, the patient is given some radioactive molecules that are called trackers. These trackers provide measurements about some activities such as glucose consumption in different parts of the brain. Different activities may be measured by using different trackers.[23] Fluorodeoxyglucose (FDG) and amyloid PET scanning are special PET scanning types as biomarkers in AD. Fluorodeoxyglucose consumption is at different levels in people with AD compared to normal individuals. Imaging these differences may provide early diagnosis. It is possible to detect AD from different types of dementia with the FDG-PET test, unlike MRI. Amyloid PET scan focuses on detecting amyloid plaques that cause AD. Alzheimer's disease is associated with amyloid plaques. Thus the amyloid PET scan may be used as a biomarker for AD diagnosis.[24]

Cerebrospinal fluid completely covers the brain and protects it by creating a barrier between the

brain and body. It provides nutrients and chemical molecules that are necessary for the brain and keeps it healthy.[25] Levels of protein that are necessary for the brain and changes in these levels may be detected in CSF, and in this way, CSF tests can be used in the diagnosis of AD. Molecules that cause AD such as β-amyloid and tau proteins are especially examined in CSF measures for AD diagnosis. Any increase in levels of these proteins may cause AD.[26]

There are also some blood tests. Magnetic resonance imaging, PET, and CSF test may be more expensive than blood tests. So it is more profitable than using blood tests as a biomarker for AD instead of MRI, PET, and CSF tests. Blood tests are used to measure molecules that cause AD-like the other biomarkers.[27]

PARKINSON'S DISEASE

Parkinson's disease occurs with degeneration in motor neurons of the central nervous system. Cell deaths occur especially in dopaminergic neurons that are found in substantia nigra, located in the midbrain, in PD.[28,29] Approximately, %80 of these neurons had been dead before symptoms occurred. The most common symptoms of the disease are rigidity in muscles, tremors, slowness of movement, and difficulty in walking.[30,31] Also, cognitive symptoms are seen such as depression, anxiety, and dementia.[32]

The exact cause of PD is not known. Nevertheless, there are some theories. It is considered that both genetic and environmental factors have effects on the occurrence of the disease. Approximately, %15 of people with PD have a first-degree relative with PD. This raises doubts about the genetic role of the disease.[33] Scientists still investigate the effect of genetics on PD. Environmental factors have a greater impact. Pesticides, herbicides, and heavy metals have a risk-increasing effect on PD. Because some components of these materials have toxic effects. These toxins may cause PD. Besides risk-increasing factors, it is considered that coffee, tea, and tobacco have risk decreasing effects. Consuming these nutrients may decrease PD.[34]

Dopaminergic neuron deaths cause PD. Some mechanisms may cause these cell deaths. One of them is about Lewy bodies. Lewy bodies are made up of α-synuclein proteins. They occur when these proteins are misfolded.[35] These proteins may accumulate in neurons and cause dysfunctions and even neuronal death. As a result of neuronal death, decreasing amounts of neurotransmitters such as dopamine and acetylcholine are seen.[36] Another mechanism is autophagy. Autophagy is a process by which the body removes degenerated and dead cells. Changes in the autophagy mechanism may cause the death of healthy cells and this may cause PD.[36,37]

The biomarkers used in PD can be examined in two groups chemical and imaging biomarkers. Biochemical biomarkers are measured by using samples from body fluids such as CSF and blood plasma. One of them is the 8-hydroxy-2′-deoxyguanosine (8-OHdG) molecule that occurs by oxidation of the 8-hydroxyguanine (8-OH-G) molecule by reactive oxides. Reactive oxygen types may react with molecules in the body and may cause neurodegeneration. The formation of the 8-OHdG molecule is a sample for this situation. It is observed that the amount of 8-OHdG in CSF in people with PD is higher than in normal people. Also, the 8-OHdG molecule is associated with deoxyribonucleic acid (DNA) damage and it is a biomarker for DNA damage.[38] PD can be diagnosed by measuring levels of this molecule.[39,40]

Another chemical biomarker is the orexin hormone. It is also known as hypocretin. It is considered that orexin regulates the sleep-wake cycle. This hormone is secreted from lateral and posterior neurons of the hypothalamus.[41] In people with PD, the level of this hormone is lower than in normal people. Since PD causes the death of the cells that produce orexin. Also, information about the severity of the disease can be obtained due to the level of the orexin hormone. The level of orexin can be measured with a CSF sample.[39]

It is mentioned that PD damages the dopaminergic neurons. Dopamine is a neurotransmitter and it is used as a precursor for noradrenaline and adrenaline. The amount of dopamine decreases when dopaminergic neurons get damaged or die. Thus, the dopamine amount is lower than the normal level in people with PD. Dopamine amount can be measured by using CSF and blood tests.[41,42] Parkinson's disease is associated with α-synuclein protein. Accumulating or misfolding this protein form the basis of the pathology of the disease. Thus, the α-synuclein amount in CSF and blood plasma is higher than normal people in people with PD. Determining these increases may provide to the diagnosis of PD.[39,43]

Besides the chemical biomarkers, imaging biomarkers are used to diagnose. Magnetic resonance imaging, PET, and single-photon emission computed tomography (SPECT) are some of them.[39] Using MRI in the diagnosis of PD is similar to AD. It aims to diagnose the diseases by imagining atrophy in

substantia nigra.[44] In PET scans, dopamine amount is controlled by using appropriate trackers. Low amounts of dopamine can be detected by PET in people with PD.[45] Single-photon emission computed tomography and PET work similarly. It aims to detect the loss of dopaminergic neurons by using radioactive trackers. Also, SPECT can provide three-dimensional imaging. Detecting loss of dopaminergic neurons may also provide early diagnosis. Radioactive trackers that are used in SPECT have a longer lifespan than those used in PET. However, trackers used in both imaging techniques are so short-lived that they disappear from the body within a day.[39,46]

HUNTINGTON'S DISEASE

Huntington's disease is an inherited neurodegenerative disorder. The general onset age of the disease is between 30 and 50 years. However, it may occur outside of this age range. It has physical and psychiatric symptoms. Involuntary movements are one of the characteristic symptoms of the disease. In the early stages of the disease, these movements are seen as simple twitches in the face and hand muscles but in the later stages, they intensify. Patients have difficulty with walking and balance problems. This progress continues until the patient finally loses his speaking and walking abilities. Generally, psychiatric symptoms appear before physical symptoms. The most common psychiatric symptoms include depression and apathy. In addition, irritability is also observed at the beginning of the disease.[47,48]

Huntington's disease occurs as a result of a mutation in the HTT gene that encodes the huntingtin protein (Htt). Huntington's disease is caused by the increase in the repeat of the cytosine-adenine-guanine (CAG) sequence, which occurs in a part of this gene close to the starting point, due to mutation. The safe number is a maximum of 35 repetitions, while the number of repetitions can vary from person to person. Over 40 repetitions cause HD, while 36-40 repetitions are the gray area to show the disease. This mutation is present in both the brain and sperm cells of the patient. This makes the disease hereditary. These high numbers of CAG repeats have a toxic effect associated with HD physical symptoms. In other words, the main cause of this disease is the mutated Htt.[49]

The magnetic resonance imaging technique leads to biomarkers used for the diagnosis of HD. Magnetic resonance imaging is used to image the atrophy in HD as in the other two diseases. Especially striatal atrophy is important evidence for HD. Also, atrophy can be seen in the thalamus and hippocampus to a lesser degree.[50,51]

Positron emission tomography imaging technique is also used as a biomarker for HD, similar to its use in other diseases. Huntington's disease is tried to be diagnosed by examining glucose metabolism as in AD with appropriate tracers. It has been observed that glucose consumption is lower in HD patients. This provides the diagnosis of HD.[50,52] The main cause of HD is the huntingtin protein that is synthesized as a result of mutation. The presence of this protein is evidence of HD. This protein can be determined also in CSF and blood plasma samples. Besides Htt protein, the neurofilament light chain (NfL) has also been observed to damage neurons. The neurofilament light chain is an axon cytoskeleton protein in neurons. An increase in the amount of this protein has been associated with neuronal damage. Therefore, it can be used as a biomarker by measuring with CSF and blood tests.[53]

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis is a subtype of motor neuron disease (MND). It occurs with the death of motor neurons that control voluntary muscles. Amyotrophic lateral sclerosis is the most common type of MND. Unfortunately, there is no known definitive treatment for ALS.[54,55] Early symptoms of the disease include motor neuron dysfunction, such as muscle weakness and problems with speech and swallowing.[56] In the last stages of the disease, it can cause paralysis and can lead to death due to respiratory failure.[57] The disease is thought to occur due to both genetic and environmental causes. About 10% of cases are genetic, the remaining 90% are sporadic and the exact causative factor of the disease is not yet known.[58] The main pathological cause of the disease is the death of motor neurons in the cerebral motor cortex, brain stem, and spinal cord.[59] For this reason, atrophy may occur in these areas. These neuron deaths have been associated with Bunina bodies. Bunina bodies are formed by the aggregation and accumulation of transactive response DNA-binding protein 43 (TDP-43). In addition, as in other neurodegenerative disorders, misfolded proteins can also be included in the pathology of the disease.[56,60]

Biomarkers are used for the diagnosis of ALS. Some of these are provided by muscle strength measurements. Two important tests for muscle strength measurements are used. The first is the maximal voluntary isometric contraction (MVIC). It is a frequently used method for diagnosing ALS and allows us to obtain good quantitative measurements

of muscle strength. Also, it has expensive equipment and consists of long test processes. Another muscle measurement test is the hand-held dynamometry test. This test takes less time than MVIC, approximately 5-10 minutes, and requires no equipment. In addition, its use in clinical studies is limited due to its low sensitivity to changes in muscle strength.[61,62] There are chemical tests as well as muscle strength tests. Cerebrospinal fluid tests are the most important measurements, as in most central nervous system diseases. It is mentioned that TDP-43 protein forms the basis of the pathology of ALS disease. Therefore, the value of this protein is higher than normal in the CSF of ALS patients. Thanks to CSF measurements, high-value detection is very important in the diagnosis of the disease.[63]

In conclusion, neurodegeneration is currently known as an irreversible process. Therefore, there is no clear and definitive treatment for neurodegenerative disorders. Thus, it is necessary to understand these diseases well and take precautions before the disease starts, and intervene if possible. At this point, diagnosis plays a very important role. Especially thanks to early diagnosis, the disease can be tried to be prevented by applying slowing or stopping methods while the disease has not progressed yet. Biomarkers are the most efficient approach for guiding us. Early diagnosis of diseases can be achieved, with the help of biomarkers. Diseases can be prevented before they start by inhibiting these processes after they have been identified. Developing new biomarkers is a very important factor in coping with neurodegenerative disorders and can be achieved by understanding the mechanisms of these diseases. The discovery of a new biochemical that causes disease also implies the identification of a new biomarker. Aside from treatment methods for various disorders, diagnostic methods are crucial, with biomarkers playing a significant role in diagnosis.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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