Available online on 15.4.2022 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

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Review Article

Review on the Different Approach between Alzheimer's and Parkinson's Disease

Cheolin Park[1], Do-Yeon Won[2] and Jae-Eun Jung[2]

[1]Dept. of Biomedical Laboratory Science, Daegu Health College, Korea
[2]Dept. of Radiological Science, Daegu Health College, Korea

A B S T R A C T

Alzheimer's and Parkinson's disease are disorders which are commonly affects the brain. However, Parkinson's disease affects the speed of thinking and memory including cognitive functions, whereas Alzheimer's affects memory and words. With this reviewed article, this information about two disorders which are very seriously in modern disease will help you prepare for a healthy 100-year-old.

Keywords: Alzheimer, β-amyloid, tau protein, Parkinson, dopamine

A R T I C L E I N F O: Received; 26 Jan 2022 Review Complete; 10 March 2022 Accepted; 26 March 2022 Available online; 15 April 2022

Cite this article as:

Park C, Won DY, Jung JE, Review on the Different Approach between Alzheimer's and Parkinson's disease, Asian Journal of Pharmaceutical Research and Development. 2022; 10(2):52-58. **DOI:** http://dx.doi.org/10.22270/ajprd.v10i2.1111

***Address for Correspondence:**
Cheolin Park, Dept. of Biomedical Laboratory Science, Daegu Health College, Korea

INTRODUCTION

It is almost true that the body's function gradually degrades as well brain's function with age. In particular, some people suffer from brain diseases such as Alzheimer's and Parkinson's disease, so-called dementia, as the brain's function regresses, but more seriously, the onset of these symptoms occurs earlier. However, although various causes such as stress, environmental factors, genetic factors, and aging have been identified, daily food or activities can improve brain cognitive abilities and prevent the brain from shrinking. Eventually, if the brain is left unused, its excellent functions gradually decline and lose their functions.

Damage to the brain can affect many things, including memory, sensation, and even personality. Brain diseases include all conditions or disorders affecting the brain. In fact, the diseases belonging to these brain diseases are very diverse and their symptoms are different, so it is important that knowing of various brain disease symptoms in advance and appropriate coping methods depending on the situation.

In particular, in order to maintain a healthy life for a long time according to the results of various studies that increase the incidence of brain diseases in old age, immediate response and preparation through information and understanding of the disease will provide a healthy life through rapid treatment. By comparing and analyzing Alzheimer's and Parkinson's disease, which are typical degenerative brain diseases, we intend to provide a desire to maintain a healthier life.

What is Alzheimer disease?

Alzheimer's disease is the most common degenerative brain disease causing dementia, and was first reported in 1907 by a German psychiatrist and neuroanatomist, Dr. Alois Alzheimer[1]. Alzheimer's disease is characterized by a very slow onset and a gradual progression. In the early stage, it mainly shows problems in memory for recent events, but as it

progresses, it is accompanied by abnormalities in various other cognitive functions such as language function and judgment, and eventually all functions of daily life are lost[2].

In the course of Alzheimer's disease, not only cognitive decline, but also psycho-behavioral symptoms such as personality changes, agitation, depression, delusions, hallucinations, increased aggression, and sleep disturbance are common. Or even physical complications such as urinary incontinence, infection, and pressure sores may appear[3].

Action mode of Alzheimer's disorder

The exact mechanism and cause of Alzheimer's disease are not known[4]. Currently, a small protein called beta-amyloid is known to have a harmful effect on brain cells as it is deposited in the brain[5], but in addition, hyperphosphorylation[6], inflammatory reactions[7], and oxidative damage of tau protein[8], which play an important role in maintaining the skeleton of brain cells, also contribute to brain cell damage. Neuritic plaques[9] (or senile plaques), a representative brain pathology finding, are associated with the deposition of beta-amyloid proteins[10], and bundles of nerve fibers are associated with the hyperphosphorylation of tau protein[11].

In addition, mutations in the amyloid precursor protein gene[12] (located in chromosome 21), the presenilin 1 gene (located in chromosome 14), and the presenilin 2 gene (located in chromosome 1)[13] are known to cause family Alzheimer's disease, but most of them are initial Alzheimer's disease.However, all of them are involved only in the onset of early-onset (elderly) Alzheimer's disease, which occurs in the 40s and 50s, and are not related to the onset of most late-onset (old-age) Alzheimer's disease.

Symptoms of Alzheimer's disease

Memory loss is one of the most common symptoms of Alzheimer's disease[14]. Symptoms such as repeated questions about recent conversations, frequent forgetting of appointments, and inability to remember recent events or events appear. In the early stages, personal information (family name, address, place of birth, school of origin, occupation, etc.) and memories of the old past are relatively well maintained, but as the disease progresses, even these are gradually forgotten[15].

The second symptom is decreased language ability[16].In the early days, when trying to speak, the appropriate word does not come to mind, so it is expressed as a pronoun such as "it, that," or there are symptoms of "difficulty finding words" that hesitate to speak and become speechless. However, as the disease progresses gradually, it becomes difficult to express it in words, and the words are reduced, and the other person's words are not well understood.

The third is decreased ability to grasp spacetime (orientation)[17].The ability to recognize time, place, or person is called orientation. In the early stages, the ability to align with time is reduced, and symptoms of not knowing the date or day of the week appear, and gradually, important anniversaries or family events cannot be taken care of. If it gets worse, they may not be able to understand the year or season, confuse day and night, and wake up at dawn to cook.

The fourth is decreased judgment and ability to perform daily life[18].As the disease progresses, the ability to think abstractly, solve problems, and make appropriate decisions or judgments decreases. Therefore, it becomes difficult to plan or make decisions and carry out tasks properly, making it difficult to manage large amounts of money, travel or socialize, or engage in professional activities.

In addition to cognitive dysfunction, so-called 'psycho-behavioral symptoms' such as personality changes, agitation, depression, delusions, hallucinations, increased aggression, sleep disturbance, apathy, and apathy are commonly accompanied[19].

What is Parkinson's disease

Parkinson's disease is the second most common degenerative brain disease after dementia[20]. There are several neurotransmitters in our brain, among them dopamine, a neurotransmitter essential for movement[21]. Parkinson's disease is a disease in which the nerve cells that secrete dopamine in a specific part of the brain called the substantia nigra[22] located in the midbrain are gradually lost without cause. It mainly affects older people, and the risk of getting it increases with age. The incidence is known to be 1 to 2 per 1,000 people, and about 1% of those over 60 years old and about 2% of those over 65 have Parkinson's disease[23].

Dementia refers to a state in which a person's mental abilities and the ability to engage in social activities are lost. This is not a diagnosis that speaks of an activity in itself, but a syndrome that refers to a case where certain criteria are met by the appearance of specific symptoms[24].

Action mode of Parkinson's disorder

Dopamine is one of the neurotransmitters produced in the body, and is a precursor to the synthesis of norepinephrine and epinephrine and plays a role in transmitting the excitation of brain nerve cells[25]. Dopamine is produced in several areas in the midbrain, including the substanitia niga (which controls movement) and ventral tegmental area as well

as hypothalamus. Dopamine is a hormone with the molecular structure of 3,4-dihydroxyphenethylamine ($C_8H_{11}NO_2$), which is a kind of catecholamine. It is supplied to various dopamine receptors in the brain called D1, D2, D3, D4, and D5 to perform various brain functions[26].

Parkinson's disease is a neurodegenerative disorder that affects movement. It occurs due to low levels of dopamine in the area of the brain that facilitates movement[27]. Without sufficient dopamine, the brain is unable to transmit signals to correctly coordinate movement.

The generated dopamine moves to the synaptic bag (the junction between neurons and cells) and enters the axon terminal. When dopamine reaches the axon terminal, the voltage-gated Ca^{2+} channel opens, increasing the intracytoplasmic Ca^{2+} concentration, and dopamine in the synaptic bag is released to the outside and released[28]. Released dopamine binds to cell membrane dopamine receptors and acts. However, in patients with Parkinson's disease, the amount of dopamine is reduced, so dopamine receptors gradually decrease. Since dopamine, which should be secreted, is not secreted, the nerve with the receptor that recognizes it also gradually degenerates[29].

Dopamine cannot pass through the blood-brain barrier (BBB) due to a large molecular structure[30]. This BBB is the connection site between the blood vessels and cells of the brain and since all the substances in the blood vessels must not enter the brain, large molecules such as dopamine cannot enter the brain. That is why dopamine cannot be used directly to treat Parkinson's disease.

Therefore, a substance called L-DOPA, a precursor of dopamine, is used to treat Parkinson's. In other words, since L-DOPA has a small molecular weight and can pass through the BBB, it is synthesized into dopamine in the brain and supplied to brain cells[31]. This is a substance called L-DOPA, that is, Levodopa[32], which is a drug for the treatment of Parkinson's disease.

There is also a theory that characterized by the abnormal accumulates of proteins into lumps known as Lewy bodies[33]. This Lewy body dementia is a type of progressive dementia that leads to a decline in thinking, reasoning and independent function because of abnormal deposits that damage brain cells for a long period.People who have Lewy bodies in their brains also have the plaques associated with Alzheimer's disease[34].

Symptoms of Parkinson's disease

The main symptoms of Parkinson's disease are movement disorders such as tremor (slow movement), tremors at rest, and muscle stiffness[35]. Without proper treatment for Parkinson's disease, movement disorders gradually progress, making it difficult to walk and sometimes even to be unable to perform daily activities at all.Bradykinesia (slow movement, bradykinesia) refers to a state of slow movement[36]. In addition to slow steps and hand movements, speech becomes slower, facial expressions disappear, and various movements of daily life such as washing face, makeup, bathing, eating, and dressing become slower. Parkinson's disease often starts first on either the left or right side, so it is often observed that patients shake one arm less when walking. Resting tremor appears as a regular tremor in the relaxed arm, and in the initial stage, the person may not be aware of the hand tremor. The tremor often goes away immediately when you raise your arm or grab an object with your hand. In general, since people have their arms relaxed when walking, tremors at rest are often observed while walking. Also, in many patients, stooping posture and narrowing stride length lead to frequent gait. As the disease progresses, balance is disturbed and falls frequently[37].

Because Parkinson's disease starts very slowly and progresses little by little, it is difficult to know exactly when the disease started. Many patients complain of other vague symptoms several years before the onset of the three important characteristic symptoms of Parkinson's disease (tremor at rest, muscle stiffness). Symptoms may include constant tiredness, weakness, discomfort in the limbs, irritability and irritability[38].

As described above, many of the symptoms that appear mainly in Parkinson's disease are related to motor function. However, other abnormal symptoms are often accompanied. These symptoms are called non-motor symptoms. Non-motor symptoms include autonomic nervous system symptoms (orthostatic hypotension, urination disorders, sexual dysfunction), gastrointestinal disorders (drooling, swallowing disorders, constipation), cognitive dysfunction (mild cognitive impairment, dementia), depression, anxiety, impulse control disorders. These include psychiatric symptoms (hallucinations, delusions), sleep disorders (REM sleep disorders, insomnia, daytime sleepiness), pain, fatigue, and olfactory disorders[39].

Different Approach

MRI (Magnetic Resonance Imaging) can provide detailed images that can be used to track many varieties of degenerative diseases, including Alzheimer's. There is no difference from the normal brain in the early stages, as a patient develops Alzheimer's disease, the brain begins to atrophy[40]. However, conventional MRI cannot structurally diagnose Parkinson's disease from normal brain[41].

Alzheimer's has no motor symptoms, and the main symptoms are disorders from memory, judgment, spatiotemporal ability, calculation ability, and

behavior. On the other hand, in Parkinson's disease, motor symptoms appear first, and symptoms such as slow walking, expressionless expression, and falling appear repeatedly[42].

Specifically, Alzheimer's dementia refers to the abnormal accumulation of beta-amyloid and tau proteins in the brain, which destroys brain cells. At first, it worsens cognitive function, and as it accumulates gradually, it worsens even motor symptoms. On the other hand, Parkinson's disease is a disease in which brain cells are destroyed due to the accumulation of a protein called alpha synnuclein[43]. As a result, abnormalities appear only in motor symptoms in the early stages, but after 10 to 15 years, the cells responsible for cognitive functions deteriorate and develop into Parkinson's type dementia.

In particular, Parkinson's type dementia is divided into two types: dementia caused by primary Parkinson's disease and Lewy body dementia[44].

Both have the same pathology, but the difference is that the location of the alpha synuclein protein[45] accumulation is different. In primary Parkinson's disease dementia, only motor symptoms appear in the early stages because protein accumulates only in motor symptom-related parts.

On the other hand, in Lewy body dementia[46], proteins accumulate in both motor symptoms and cognitive domains. Therefore, cognitive behavioral symptoms such as hallucinations and hallucinations appear at the same time as Parkinson's disease.

However, there are differences in the causes of brain damage. Alzheimer's is caused when a protein called amyloid, which damages tissue, accumulates in the brain, whereas in Parkinson's, cells that produce neurotransmitters in the substantia nigra degenerate and brain function is slowed[47].

Alzheimer's disease begins at the surface of the brain and spreads to the depths of the brain, whereasParkinson's has a different pattern because it starts deep in the brain and spreads to the surface of the brain[48].

Alzheimer's is characterized by deterioration of memory and cognitive abilities. Memory, judgment, ability to sense time and space, and calculation ability are impaired, which leads to hallucinations, paranoia, and inability to distinguish between day and night.On the other hand, Parkinson's disease first appears as a body movement disorder. Trembling symptoms appear when the body is relaxed, and after time passes, stiffness in muscles occurs. And the movement slows down and the posture becomes unstable[49].

Parkinson's disease causes physical abnormalities, resulting in dysphagia, defecation disorders, and sweating due to autonomic nervous system[50]abnormalities, resulting in a lot of skin problems.

And when Alzheimer's progresses significantly, similar to Parkinson's, bowel and urine disorders, body stiffness, and gait disorders occur[51], and Parkinson's disease also causes cognitive impairment. However, Parkinson's is characterized by severe ups and downs in cognition[52].

Therapeutic approach

Parkinson's disease affects the nervous system, including the brain. As a result, many people with Parkinson's suffer from depression, hallucinations, mental or emotional problems, and difficulty concentrating on their thoughts[52]. Early patients often accept these symptoms as simply a psychological problem, and often do not recognize that it is a symptom of Parkinson's disease.

The treatment of Parkinson's disease is basically drug therapy. There are several types of Parkinson's drugs, but dopamine drugs are the most effective. However, when dopaminergic drugs are used for a long time, late motor complications may occur[53].

Practicing together with drug treatment as a basis, the reduction of toxic protein can be a good treatment method[54]. When exposed to stressful environments, the body produces toxic proteins, which damage nerve cells. In other words, stress[55] is one of the factors that greatly influence the onset of Parkinson's disease, so it is a good way to receive concurrent treatment with a program that improves breathing exercise, diet, and sleep so that toxic proteins are not produced.

Parkinson's treatment drugs are drugs that do not cure Parkinson's disease or stop the progression of Parkinson's disease, but supplement the lack of dopamine so that the patient can perform well in daily life. No drug has yet been developed that regenerates dopaminergic neurons or delays the loss of dopaminergic neurons. The most representative Parkinson's drug currently in use is levodopa, a precursor of dopamine[56].

Levodopa[57] is absorbed from the gastrointestinal tract, moves to the brain, and is converted into dopamine to supplement dopamine deficiency in the brain of a Parkinson's patient.In addition to levodopa, dopamine agonists, a substance similar to dopamine, and dopamine-degrading enzyme inhibitors[58], a substance that allows dopamine to remain in the body for a long time, are used.

There are two types of dementia drugs commonly used: cholinesterase inhibitors[59] and N-methyl-D-aspartate antagonists[60]. In June 2021, Aduhelm (Aducanumab)[61], the world's first FDA-approved treatment for Alzheimer's dementia, was approved. It is said that aducanumab is a causative agent that inhibits the progression of the disease or

fundamentally blocks the occurrence of the disease and reduces beta-amyloid plaques.

This is a disadvantage that although amyloid beta protein, which worsens symptoms of Alzheimer's disease, can be effectively removed within brain tissue and fundamentally removed in advance, it cannot be expected to have a great effect on severely ill patients who have already progressed[62].

However, in the brain of Alzheimer's patients, besides amyloid protein, there is a neurotoxic substance called nerve fiber bundle[63], which is not known to be removed. Acetylcholine[61] is a substance closely related to brain function in Alzheimer's disease. In the brain cells of dementia patients, the number of cholinergic neurons is reduced, and the concentration of acetylcholine is also lowered. Cholineesterase inhibitors[64] are effective by inhibiting choline esterase, which decomposes acetylcholine, to increase acetylcholine concentration.

Among the representative drugs, Donepezil (Arycept), Rivastigmine (Exelon), and gallantamine (leminyl), Donepezil[65] is the most commonly used drug. It does not cure Alzheimer's disease, but it may improve memory, awareness, and the ability to function. This medication is an enzyme blocker that works by restoring the balance of natural substances (neurotransmitters) in the brain.

Rivastigmine[66] as a cholinesterase inhibitor is used for the treatment of mild to moderate state and also adapted when it is difficult to swallow food or has a severe gastrointestinal disorder due to patching. In other words, the principle is to block acetylcholine degradation enzymes, even if the number of synapses decreases due to Alzheimer's, so that acetylcholine, a more neurotransmitter, exists in fewer synapses.

Galantamine[67] is used to treat mild to moderate dementia (memory loss and mental changes) of Alzheimer's disease. This does not cure Alzheimer's disease, and it will not stop the disease from getting worse.

Next is NMDA receptor antagonists[68], which are treated by reducing the amount of brain chemicals called glutamate. This helps slow the damage to brain cells affected by Alzheimer's disease and is known to slow the progression of symptoms. This drug is moderate dementia and is used when drugs such as Donepezil are not available or have severe Alzheimer's disease for some reason.

The progression of Alzheimer's dementia is related to a neurotransmitter called glutamate, and excessive secretion of glutamate causes problems in the calcium ion pathway of nerve cells, and taking Memantine[69] (NMDA receptor antagonist) prevents excessive calcium from entering the cell.

However, the above-mentioned drugs do not work in the production or accumulation of beta-amyloid or tau protein, so they do not inhibit the progression of dementia.

In addition, not only the mentioned above drugs, but also therapeutic drugs for abnormal behavior are used. Neurotic laxatives[70] are used when aggressive, swearing, and hyperactivity are severe, and antidepressants or anticonvulsants are used when depression and emotional ups and downs are present. In addition, sedative sleeping pills[71] are sometimes used for sleep disorders or nighttime behavior. Other approaches to treating Alzheimer's can improve the quality of life by providing various programs such as work therapy and cognitive function reinforcement therapy that allow patients to maintain basic daily life as much as possible[72].

CONCLUSION

It is true that the incidence of dementia and Parkinson's disease increases with age. However, just as not all elderly people are dementia patients, 80-year-old elderly people are healthy and active in social activities, while 50-year-old middle-aged people suffer from dementia. The idea of "everything is like that when you get older" about dementia is wrong common sense. Dementia is not just an aging phenomenon, but a disease.There is no secret to preventing dementia 100%. However, regular exercise, brain cognitive activity, and eating appropriate food can delay and prevent the onset of dementia.

Parkinson's disease is difficult to expect complete recovery, but early detection with appropriate medications can improve symptoms as well as quality of life, so it is important to respond quickly with early symptoms.

Stress occurs due to unnatural body movements, and various problems may appear as a result. To prevent Parkinson's disease, regular exercise can help. Even if already have Parkinson's disease, it is good to manage physical activity by regular exercise such as careful walking. As Parkinson's disease progresses, the lower back can bend or the joints become stiff, so exercise to improve the usefulness of the body can also be helpful.

During daily life, the brain should be stimulated positively through hobbies, and appropriate exercise should be performed at least 3 times a week according to physical fitness. In addition, dietary intake should be accompanied by nutrients such as antioxidant foods, vitamin-rich green and yellow vegetables, DHA-rich blue-green fish, and nuts. Only then will you be able to live a healthy life for 100 years old.

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