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Neurodegenerations are diseases of the present and the future

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Summary

Neurodegenerations are diseases of the present and the future. As the human population grows, the number of people suffering from neurodegenerative diseases will increase. Neurodegenerations diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, spinocerebellar ataxia, spinal muscular ataxia), sporadic (amyotrophic lateral sclerosis) or infectious (prion disease). Nerve cells (neurons) can't regenerate and therefore die under the influence of pathological factors. Neurodegenerations diseases can be serious or life-threatening. It depends on the type. Drags and treatments may help improve symptoms, relieve pain, and increase mobility.

Key words: Neurodegenerations, Alzheimer's disease, Parkinson's disease, Huntington's disease, spinocerebellar ataxia, spinal muscular ataxia, sporadic (amyotrophic lateral sclerosis) or infectious (prion disease).

Introduction

Due to the changing demographics of the human population, there is an increasing chance that we will develop diseases related to neuronal damage.

Neurons are part of the nervous system that cannot regenerate, therefore when they are affected by damaging factors (pathological forms of proteins), they die.

The main neurodegenerative diseases in the Polish population are dementias (most often Alzheimer's disease) and movement disorders (Parkinson's disease).

Degenerative diseases are closely related to age (Parkinson's and Alzheimer's disease) - the older the population, the greater percentage of people become ill. These conditions can be hereditary (Huntington's disease, spinocerebellar ataxia, spinal muscular ataxia), sporadic (amyotrophic lateral sclerosis) or infectious (prion disease).

The main symptoms of neurodegenerative diseases are progressive dementia or movement disorders.

Neurodegenerative diseases are a group of inherited or acquired disorders of the nervous system, the essence of which is the loss of nerve cells. This process begins with an asymptomatic phase that may precede clinical symptoms for many years.

Statistics of the incidence of neurodegenerative diseases

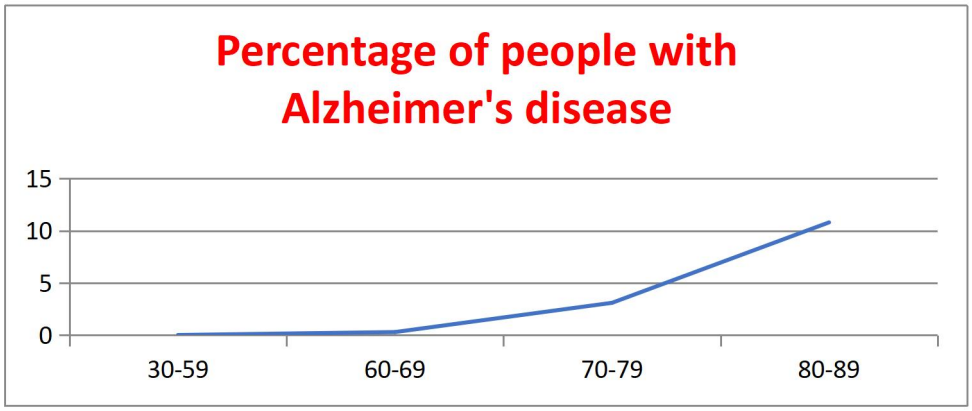
In July 2021, the Central Statistical Office published data on the average life expectancy of Poles. They show that the average life expectancy of men was 72.6 years, and that of women - 80.7 years (Dementia in Europe Yearbook 2019 Estimating the prevalence of dementia in Europe, 2019) . There has been a steady increase in the statistical life expectancy since the mid-nineteenth century. It will also increase in the future, but it is not known at what rate. According to the report of the Central Statistical Office on Alzheimer's disease in Poland, over 65 years of age currently makes up approx. 14.7% of the population, in 2035 it will increase to 24.5%, and in 2050 it will reach over 30%. Currently, there are over 300.000 diagnosed and undiagnosed people with Alzheimer's disease in the country.

This is a significant number, and it should be remembered that the disease also affects caregivers and the entire families of patients. By 2050, the number of patients will triple and reach almost a million (Braak H, 2012) . In Europe, about 10 million patients suffer from Alzheimer's disease, and by 2050 this number will almost double.

In Europe, the incidence of Alzheimer's disease by age is presented in Table 1 and Figure 1a below.

Table 1 The prevalence of dementia in Europe

Age	Percent
60–64	0.6
65–69	1.3
70–74	3.3
75–79	8.0
80–84	12.1
85–89	21.9
90+	40.8



Picture 1 The prevalence of Alzheimer's disease in Europe (EURODEM Prevalence Research Group)

Parkinson's disease is the next - after Alzheimer's disease - most common neurodegenerative disease in the global population. In Europe, around 1.6% of people over the age of 60 have Parkinson's. According to estimates, there are approximately 60-80 thousand patients in Poland, and each year there are approximately 4-8 thousand new cases of this disease 1 (Von Campenhausen S., 2005).

Huntington's disease affects 5-10 people out of 100.000 (Pringsheim T., 2012), (Bates G., 2002)

A similar incidence applies to ALS (5-10 people per 100.000). Usually middle-aged and elderly people are sick.

In prion disease, the incidence is 1 per million (Nowacki P., 2019).

Another neurodegenerative disease is spinal muscular atrophy (SMA), which affects 10 people per 100000 births (Saniewska N., 2019).

Alzheimer's disease

Alzheimer's disease is the most common cause of dementia.

The clinical symptom of this disease is progressive disturbance of cognitive functions (memory, thinking, language functions) and post-cognitive functions (behavioural and psychotic disorders).

Pathological proteins beta-amyloid extracellularly and tau protein intracellularly accumulate in the neurons of Alzheimer's disease patients. This leads to the destruction of neurons, cortical synapses and certain subcortical areas. This phenomenon is many years ahead of the onset of clinical symptoms of the disease. The atrophy of the cerebral cortex mainly affects the temporal and parietal lobes, as well as some of the frontal lobes and gyrus (Morris J., 2003) (Hulstaert F., 1999).

This is confirmed by MRI (magnetic resonance imaging) and PET (positron emission tomography).

The basis for the diagnosis of Alzheimer's disease in a patient is the performance of screening tests to assess cognitive functions, including the Mental State Examination Scale - MMSE (Mini-Mental State Examination) and the Clock Drawing Test (CDT) (Bateman Randall J.B.R., 2007).

In addition, clinical trials investigate markers such as: β-amyloid, tau protein, and the phosphated tau protein in the cerebrospinal fluid.

In patients diagnosed with Alzheimer's disease, a decrease in the amount of β-amyloid as well as an increase in the amount of tau protein can be noticed (Mckhann G., 1984).

Age is the first risk factor to be considered. Genetic factors also influence the occurrence of this disease (Apo E gene polymorphism) (Han X., 2004). The level of education and social contacts, mood, diet rich in unsaturated fatty acids (Scarmeas N., 2009), lifestyle and accompanying diseases are also important.

The diagnosis of Alzheimer's disease in clinical practice is based on the criteria contained in the International Statistical Classification of Diseases and Related Health Problems, 10 revision, as shown in Table 2.

Table 2 Diagnostic criteria for dementia according to ICD-10 (WHO, 1993)

1	It is stated, confirmed by an objective interview and psychometric tests, the presence of:
	a. memory impairment (especially in terms of learning new information),
	b. disturbances in other cognitive functions that have worsened compared to the previous level of functioning, to a degree that significantly disrupts the proper functioning of everyday life activities.
2	There are no disturbances in consciousness during the evaluation period.
3	There is a disturbance of emotional control over motivation or a change in social behaviour, manifested by at least one of the following symptoms:
	a. emotional lability
	b. irritability
	c. apathy
	d. primitization of social behaviour
4	Memory and other cognitive dysfunction have been present for at least six months.
5	Additionally, diagnosis is enhanced by the occurrence of disorders of other higher cortical functions in the form of aphasia, agnosia, apraxia.

Alzheimer's disease develops from the 4-5th decade of life. There is a gradual degeneration of neurons, which corresponds to the different stages of cognitive impairment, which are defined by the GDS scale (Table 3).

Table 3 GDS (Global Deterioration Scale) according to Reisberg et al., 1982.

Stage of advancement	Scale description
No cognitive impairment	No subjective complaints about memory deficits.
Very mild cognitive impairment	Subjective complaints about memory deficits, most often in the following areas: (a) forgetting where we have placed familiar objects; (b) Lack of objective evidence of a memory deficit in a clinical history. No objective deficits at work or other social situations.
Mild cognitive decline (mild cognitive impairment)	Earliest significant deficits. Manifestations in more than one of the following areas: (a) the patient may have become lost while traveling to an unknown place; (b) co-workers notice a deterioration in the professional functioning of the patient; (c) unable to find words and names becomes obvious to those close to you; (d) the patient can read a passage of text or a book and remember relatively little material; (e) the patient may show diminished ease in remembering names after reading it with new people; (f) the patient may have lost a valuable item; g) memory deficits may be evident in clinical trials. Objective evidence of deterioration in memory function obtained only during intensive interviewing. Decreased performance in demanding employment conditions and social. In the patient, denial begins to manifest. The symptoms are accompanied by mild to moderate anxiety.
Moderate cognitive decline (mild dementia)	A clear deficit in a thorough clinical history. The deficit manifests itself in the following areas: (a) reduced knowledge of the current and recent events; (b) may have some memory deficit of personal history; (c) makes mistakes in subsequent subtractions (memory test item); (d) reduced ability to travel, deal with finances, etc. Often lack of deficits in the following areas: (a) orientation in time and place; b) recognizing familiar people and faces; (c) the ability to travel to famous places. Inability to perform complex tasks. Denial is the dominant defense mechanism. Affection is often shallow and withdrawn from difficult situations.
Moderately severe cognitive decline (moderate dementia)	The patient can no longer survive without the help of others. During the conversation, the patient is not able to recall an important aspect of his current life, e.g. address or telephone number, names of immediate family members (e.g. grandchildren), the name of the secondary school or university he graduated from. Often confusion about time (date, day of the week, season, etc.) or place. An educated person may have difficulty counting down from memory tests. People at this stage keep knowledge of many important facts about themselves and others. They invariably know their names and they generally know the names of their spouses and children. They do not require any help with using from the toilet and food, but may have difficulty with the selection of appropriate clothing.

Severe cognitive decline (moderately severe dementia)	The patient may sometimes forget the spouse's name, on whom his or her survival completely depends. He is largely unaware of all recent life events and experiences. Retains some knowledge of past life events, but this is very sketchy. He is generally unaware of his surroundings, of the year, season, etc. May have difficulty counting to 10, both backwards and sometimes forwards. Will require some help with daily activities, e.g. the patient may have urinary incontinence, will not be able to travel alone, but will sometimes be able to travel to previously known places. He often has a disturbed circadian rhythm. He almost always remembers his name. Often it still is able to distinguish between known and unknown people in your surroundings. There are personality and emotional changes. They are quite variable and include: (a) delusional behaviour, e.g. patients may accuse their spouse of being a cheat, they may talk to imaginary characters in their surroundings or with their own reflection in the mirror; (b) obsessive symptoms, e.g. the person may repeat simple related activities over and over again with cleaning; (c) symptoms of anxiety, agitation and even previously non-existent violent behaviour may occur; (d) cognitive a bulla, i.e. loss of willpower because the individual is unable to hold thoughts long enough to determine the deliberate course of action.
Very severe decline in cognitive function (severe dementia)	At this stage, all verbal skills are lost. Often the patient does not speak at all - at this stage of the disease, we observe only incomprehensible statements and the rare appearance of intelligible words and phrases. Urinary incontinence occurs, the patient requires assistance in the toilet and with feeding. As this stage progresses, basic psychomotor skills, such as the ability to walk, decline. The brain seems no longer able to tell the body what to do. Often there is generalized stiffness and developmental neurological reflexes.

Unfortunately, there is no causal treatment for Alzheimer's disease. We can only treat Alzheimer's dementia. Treatment is aimed at slowing the development of dementia, preventing the occurrence of psychotic disorders, and improving the daily activities of patients. Currently, pharmacotherapy includes: cholinesterase inhibitor (ChE) or / and butyrylcholinesterase inhibitor (butyrylcholinesterase inhibitor), and / or NMDA N-methyl-D-aspartic receptor antagonist (N-methyl-D-). aspartate receptor) such as rivastigmine, donepezil and memantine. This treatment is only symptomatic. Numerous clinical trials are currently underway, offering hope for a causal treatment for Alzheimer's disease.

Parkinson's disease

Parkinson's disease is the most common neurodegenerative movement disease in the Polish population. It is the second most common neurodegenerative disorder.

The clinical symptoms of this disease include psychomotor slowing, increased muscle tone and involuntary movements similar to resting tremor.

Destruction occurs in substantia nigra and other dopamine-producing pigmented areas of the brain. In the affected areas of the brain, the presence of the pathological protein alpha-synuclein with intracytoplasmic inclusions, referred to as Lewy's bodies, is found. These pathological forms of proteins that damage neurons cause their death (Stefanis L., 2012).

The basis for the diagnosis of Parkinson's disease is a clinical examination confirming the presence of muscle stiffness, resting tremor and slowness.

Imaging tests performed in this disease include: MRI of the central nervous system and scintigraphy using the DaTSCAN marker.

In addition, scientific research measures the level of α-synuclein in the plasma, which is the main component of Lewy bodies. According to studies, the increase in plasma concentration of α-synuclein oligomers turned out to be highly specific (85%) in detecting Parkinson's disease compared to the control group. Lowering the concentration of this biomarker occurs in the cerebrospinal fluid of patients with synucleinopathies (Parkinson's disease, dementia with the bodies of Levi). Patients with Parkinson's disease have an increased expression of α-synuclein also in fibroblasts (skin cells), and their concentration can be used as a diagnostic marker (Mollenhauer B, 2008) (Hoepken HH, 2008).

The risk factors for the occurrence of Parkinson's disease are: age, male sex (the effect of estrogens (Reuter I., 2019), and genetic determinants. The factors protecting against the disease are smoking and drinking coffee (Louis E.D., 2015).

There are different classifications for the severity of symptoms in Parkinson's disease:

1.Stages of Parkinson's disease are correlated with the level of dopaminergic cell loss. They are presented in Table 4. (Reuter I., 2019).

Table 4 Phase model of the division of Parkinson's disease into stages

Pre-clinical phase	Prodromal phase	Clinical phase
The lack of a marker allowing for the detection of this stage of the disease, although the neurodegenerative process continues, does not give any clinical symptoms	They appear here: 1.Disturbance of smell 2.Constipation 3.Autonomic dysfunction 4.Behavior and mood disorders 5.Disturbances during REM sleep 6.Changes in neuroimaging research	It is characterized by the occurrence of: 1. Motor symptoms: bradykinesis, stiffness, tremors, postural instability 2. Symptoms beyond movement: cognitive disorders, psychotic disorders, mood disorders, sleep disorders, sexual functions, micturition, constipation, weakness

2. Another division of the disease advancement stages was developed by Hoehn and Yahr. Their division determines the severity of motor symptoms. It has 5 steps, as shown in Table 5

Table 5 Division into stages according to Hoehn and Yahr

Grade of severity according to Hoehn and Yahr	Description
I	clearly unilateral symptoms, without or with a slight functional disability
II	bilateral symptoms, no imbalance
III	bilateral symptoms, mild to moderate intensity with limited postural reflexes, abnormal arm pull test result, the patient is still physically independent
IV	a severe disease; the patient is still there able to stand or walk without assistance
V	the patient requires the help of others, is in a wheelchair or is lying down.

3. The Unified Parkinson's Disease Rating Scale describes the mobility status and the severity of the condition. It is presented in Table 6.

Table 6 The unified Parkinson's disease rating scale

Terms	Description
The honeymoon period	the initial phase of the disease, very good mobility after the initiation of dopaminergic treatment
‘’On’’ phase	good mobility, good drug effect
"Off" phase	poor mobility, poor drug effect
Wearing-off	reduction of mobility at the end of time of dopaminergic drug action before taking the next dose
Dyskinesia	involuntary movements
Dose peak dyskinesia	involuntary movements at the time of the highest concentration of levodopa in the blood serum
Dyskinesia phase "off"	"ooneff" phase dyskinesia involuntary movements, especially of the lower limbs in the "off" phase
Dystonia	dystonia contractions of the muscles of one limb in the "off" phase, partly also in the "on" phase, causing incorrect positioning

Pharmacological treatment of Parkinson's disease consists of increasing the level of dopamine in the central nervous system, as the deficiency of this neurotransmitter is at the root of the symptoms of the disease. Pharmacotherapy is aimed at supplementing the level of levodopa or reducing the breakdown of dopamine (MAO inhibitors, e.g. selegiline and rasagiline), also drugs belonging to dopamine agonists (DA) (dopamine agonists) such as apomorphine, bromocriptine, ropinirole, pramipexole, rotigotine are used. COMT inhibitors (e.g. entacapone) are also used in the treatment.

In very advanced cases, those poorly responding to pharmacological treatment, deep brain stimulation DBS (Deep Brain Stimulation) can be used. It is a surgical method in which electrodes are implanted into the brain that affect specific areas of the extrapyramidal system (Wei Z., 2018).

It is also important to treat non-motor symptoms (psychiatric - psychotic disorders, sleep and mood disorders; internal medicine - orthostatic hypotension, constipation; neurological - cognitive disorders, dizziness). Extremely important in this disease is physical rehabilitation preventing disability and prevention against falls and injuries - adjusting the bathroom, orthotics, e.g. walking frames.

ALS - amyotrophic lateral sclerosis.

ALS is a neurodegenerative disorder of the upper and lower motor neurons.

The main symptom of this disease is muscle atrophy, manifested by fatigue, walking problems, trembling limbs, and disturbed breathing and swallowing.

The diagnostic test that confirms the diagnosis of ALS is electromyography (EMG). Neuroimaging tests are also performed, which allow for differential diagnosis.

The pathogenesis of ALS is not fully understood, it is probably multifactorial:

- superoxide dismutase (metalloprotein) hyperactivity - a free radical mechanism, i.e. neurons are damaged as a result of oxidative stress,
- glutamic acid toxicity,
- axonal transport disorders,
- rapidly degraded SOD1 mutant protein can cause loss of control of interactions between proteins and the formation of insoluble conglomerates in motoneurons (containing β-amyloid) and has a neuro-inflammatory effect,

- cytoskeleton dysfunction,
- genetic factors (Ince P.G.), (Barber S.C., 2010), (Ferraiuolo L., 2011).

The degeneration and loss of neurons in the spinal cord have different locations that define different types of motor neuron disease [Table 7].

Table 7 Variations of motor neuron disease

Amyotrophic Lateral Sclerosis (ALS)	Degeneration of the upper and lower motor neurons
Progressive Muscle Atrophy (PMA)	Only the inferior motor neuron is involved
Primary Lateral Sclerosis (PLS)	Only the upper motor neuron is involved
Progressive Bulbar Paralysis	Only bulbar symptoms or bulbar-onset ALS One-limb muscle atrophy
One-limb Muscle Atrophy.	Dominant damage to the lower motor neuron, one upper limb
Two-arm muscle atrophy.	Dominant damage to the lower motor neuron, both upper limbs

Unfortunately, there is no effective causal treatment modifying the course of ALS. A slight increase in the percentage of survival in 12- and 18-month follow-up was demonstrated by the glutamate inhibitor - orally administered riluzole (Bensimon G, 2004).

It is also possible to administer edaravon by intravenous injection. It is a drug not registered in Poland, but it can be imported to the so-called target import. It is administered in 2-week series (14 daily infusions, then 14 days off, then infusions for 2 weeks, and then rest from therapy). This drug offers hope for the inhibition of the atrophy of neurons in the anterior horns of the spinal cord (Sawada H., 2017).

ALS is a disease that inevitably leads to death. It requires multidisciplinary care, including non-invasive ventilation, physiotherapy, PEG feeding - gastric tube, in terminal states - mechanical ventilation, of course, if the patient agrees to such therapy.

Symptomatic treatment includes inhibition of drooling, spasticity and mood disorders. The support of caregivers is very important in this disease.

It is worth noting that the average survival time from the onset of this neurodegenerative disease without treatment is 3 years (Siddique N., 2001).

Huntington's disease

Huntington's disease is a genetically determined progressive neurodegenerative disorder of the nervous system. It manifests itself as movement disorders (choreic movements), dementia and mental disorders. The disease progresses as a result of the genetically programmed death of neurons in the central nervous system. A genetic marker is a gene mutation in the gene that codes for a protein called huntingtin. Excess of this protein leads to the death of neurons. Atrophy and secondary gliosis of the nervous system particularly affect the pale glue and the crust. In order to diagnose Huntington's chorea, genetic tests that confirm the mutations should be performed (Sławek J., 2013).

Changes in brain resonance are also associated with Huntington's disease.

The disease usually begins in the 4th decade of life. In the initial stages, there is awkwardness in movements, restlessness, irritability and distraction. This is followed by chorea and dementia. Very often this disease is accompanied by psychiatric disorders (psychotic symptoms, depression, carelessness). Average survival is about 15 years (Louis E.D., 2015).

For several years, therapy with tetrabenazine or deutetrabenazine has been possible. It is worth mentioning that scientists from the University of British Columbia Center for Huntington's Disease, led by Dr. Blair Leavitt, are conducting research on a new drug - pridopidine, which can restore the balance of the activity of the neurotransmitter dopamine in the brain's motor centers.

Huntington's chorea leads to disability and death, as programmed brain death is currently impossible to stop.

SMA- spinal muscle atrophy.

SMA is a neurodegenerative disorder that causes muscle wasting. It occurs at different ages, depending on the type of disease.

The 4 types differ in the age of the first symptoms, the severity of the disease and the prognosis.

Table 8 Clinical classification of SMA

Type of SMA	The highest level of motor development in case of untreated treatment	Most common observed age first symptoms
Type 1	Doesn't sit unsupported	Under 6 months of age
Type 2	Sits unsupported, does not stand	6–18 months
Type 3	Steps unsupported	From 12. Months of age
Type 4	Normal	Over 30 years of age

SMA is a neuromuscular disorder that causes the muscles to become loose.

The disease is genetically determined, inherited autosomal recessively. This condition is caused by the dying of the neurons in the spinal cord, which are responsible for how the muscles work. As a result of the disease, there is a progressive weakening of the muscles and their gradual atrophy. Depending on the clinical form, the disease affects children from the first months of life to adults after the third decade of life.

It is the only neurodegenerative disease for which, recently, causal treatment has become possible, if applied quickly enough.

In 2016, the drug nusinersen was registered. This substance modulates alternative splicing of the SMN2 gene by functionally converting it into the SMN1 gene. A mutation in the SMN1 gene causes SMA, leading to a decrease in the level of the SMN protein in the central nervous system. Nazinersen increases the level of the SMN protein, reducing the symptoms of the disease. A difficulty in administering nazinersen is the need for repeated intrathecal injections every 4 months.

Since 2019, gene therapy with abeparvovec onasemnogen is possible. It also raises the levels of the SMA protein in the motor neurons to slow the progression of the disease, but it is given only once into a vein. Since 2021, it is also possible to use Ripple in causal treatment. Bow is administered daily orally. It works by correcting the folding of SMN2 to increase the concentration of the functional and stable SMN protein.

Intrathecal or orally administered Nazinersen raises the level of the SMN protein by modifying the SMN2 gene to make it act as the SNM1 gene, and the abeparvovec onasemnogen, when administered intravenously, delivers the finished SMN1 transgene to the cells.

SMA diagnosis includes clinical, genetic and electromyographic examination. Due to the possibility of causal treatment, it is very important to diagnose this disease early in order to start an effective therapy as soon as possible.

Summary

The above-described neurodegenerative diseases seem to be the most important due to the frequency of occurrence and their social and economic consequences. However, they do not exhaust the range of diseases associated with damage to the central nervous system.

Diseases with a neurodegenerative basis include, among others, prion diseases, cerebrospinal ataxias, progressive supranuclear palsy, Alexander's disease, ataxia-telangiectasia syndrome, Refsum's disease and many others.

The prognosis for all neurodegenerative diseases is poor, as they lead to progressive failure of the nervous system functions. The symptoms of neurodegeneration are related to impairment of motor functions or memory.

Treatment is usually (only in SMA we can treat patients causally) symptomatic, it can only slow down the process of neurons dying. This situation is not optimistic, considering the fact that - due to the aging of the population - the number of patients will increase dramatically.

As the process of neurodegeneration begins with an asymptomatic phase, which may precede clinical symptoms for many years, only the initiation of treatment in the asymptomatic phase gives hope for stopping neuronal atrophy, therefore it is necessary to use early diagnosis of these diseases. Thanks to neuroimaging tests (e.g. PET), tests of the concentration of proteins in the blood and cerebrospinal fluid (beta-amyloid, tau protein, alpha-synuclein, fibronectin) and genetic tests, we can recognize some diseases
in the preclinical phase.

As life expectancy continues to rise statistically, it is expected that more people will develop neurodegenerative disorders. It remains to be hoped that thanks to preventive measures and the advancement of medicine in the future, we will be able to better cope with the consequences of these diseases.

It is worth mentioning the Nobel Prize in the field of chemistry for the so-called "Molecular scissors", which cut DNA, cut out fragments of it, or insert new ones. This modern technology also offers hope for effective treatment of neurodegenerative diseases.

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