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Parkinson's Disease: A Neurodegenerative Disease

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Abstract

Parkinson's disease is characterized by tremor, stiffness, rigid muscles, bradykinesia, slowness of movement, instability leading to falls, memory and talking difficulties, fatigue, writing modifications (micrography) and dementia. In addition, depression, urinary (bladder) problems, constipation, decreased ability to smell and sleep disruption are among the symptoms associated to the PD. As Parkinson's cannot be eradicate, treatments are oriented toward a slow decline and deterioration and therefore, only palliative care predominates. Mutations of 6 genes (SNCA, LRRK2, PRKN, DJ1, PINK1 and ATP13A2), are the cause of familial Parkinsonism. They are playing a role in the metabolism of α -synucleine, in mitochondrial control, oxidative stress, lysosomal functions, transport and recycling of proteins and immunologic activities. Five stages with increased gravity have been identified. From stage 1 to 3, symptoms may be treated with pharmacological drugs. At stages 4 and 5, the patient needs assistive help and an ambulatory walker device. L-dopa is transformed in dopamine in the brain. Treatments for speech disorders increase the disability of these symptoms. Dopamine agonists, MAO-B and COMT inhibitors contribute to help break down dopamine, an anticholinergic drug aiming to reduce tremors and muscle rigidity. Death is occurring within 7 to 15 years.

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Keywords

Parkinson's Disease; Neurodegenerative Disease; Tremor; Stiffness; Postural Instability; Speech Changes; Alpha-Synuclei; Lewy Bodies

Introduction

Parkinson's Disease (PD) displays characteristics symptoms which are the followings: resting tremor, stiffness, rigid muscles, bradykinesia, slowing of movement, speech changes, writing changes (micrography) and dementia (SNCA, LRRK2, PRKN, DJ1, PINK1 and ATP13A2) [1-12]. PD is a disease of the family of α -synucleinopathies. Lewy bodies are the second neuropathologic features of PD. PD is a chronic disease, with slow evolution, the beginning being insidious and with intermittent evolution. At the beginning, the symptoms are visible only in one side and afterward become bilateral, but stay asymmetric. Very seldom before 45 years, increasing in older, a peak is seen between 85 and 89 years. The Parkinson Disease begins firstly by a gradual degenerative change leading to the alteration of dopaminergic neurons. The degradation is associated to three essential phenomena

- An increase of the group of lesions called Lewy bodies, showing for a great part an abnormal accumulation of α synucleine structural protein, found in the midbrain or within the cortex
- An abnormal mitochondrial activity
- An inflammation of the brain, related to many groups of immunogenic microglial cells of the acquired immunity and T-lymphocytes of adaptive immunity

The α -synucleine is naturally present in humans. This abnormality diffuses gradually inside a neuron and later, moves from one neuron to another one. Neuronal populations associated with other neurotransmitters (serotonin, acetylcholine or noradrenaline) are also equally affected by synucleinopathies and neuronal degeneration. Family disease is occurring in 15% patients and a genetic origin bound to a single causal gene is found in 5% case.

Symptoms of the PD

Parkinson causes have not yet been identified. Evolution of the disease is related to the age at the onset, on the dominance and four motor symptoms are considered as cardinal signs.

Stage 1: is the mildest form of tremor, walking, facial expression and posture. Between 3 to 8 years, the patient is reactive to dopaminergic treatment

Stage 2: moderate form that can take months or years. Tremor, rigidity starting to affect one part or both side of the body. The drug medication is no more efficient

Stage 3: is the middle stage in the sickness, occurring some years after stage 1. Medication aim to decrease symptoms

Stage 4: It is an advanced stage or aggravation of the disease becoming now non-reversible. Tremor troubles, cognitive problems, memory loss and depression. There is a need of assistive help such as dressing or using a walker

Stage 5: There is a need of assistive help. It becomes harder to life alone

Genetic Causes of PD

About 20 genes are associated to monogenic forms and about one hundred increase the risk of aggravation of the disease. Genes implicated are playing a role in the metabolism of α -synucleine (SNCA, LRRK2, GBA), mitochondrial control (Parkin, PINK1, FBXO7), oxidative stress (DJ 1), lysosomal functions (ATP13A2, GBA), transport and recycling of proteins (VPS35, LRRK2) and immunologic activities (LRRK2, PRKN/Parkin, PINK1). They may be recessive or dominant, depending of the age at which the disease is diagnostiqued. Initial therapy undertaken with medications aiming to treat hallucinations, delusions and dementia. In younger patients (55 à 65 years); the expecting for survival is around ten years (13-14 years), with more male than female (ratio around 3:2). Neurodegenerative diseases called synucleinopathy are due to abnormal accumulation of alpha-synucleine in the brain. Neuropsychiatric problems are detected though smell and sleep alterations focusing on the age at the onset of the disease, on the dominance and for PD tremor, slowness of movements (bradykinesia), rigidity and postural instability.

Non-genetic Causes of PD

Defectives mitochondrias are normally destroyed, a process called mitophagy. Défectives mitochondrias might survive and favor production of ROS. The evidence linking mitochondrial dysfunction to neurodegenerative disorders and, in particular, PD is impressive [2].

Drugs, such as prasinezumab, seem to be promising in reducing the production of alpha-synucleine and its aggregating properties, utilizing small molecules interacting with non-aggregating forms of alpha-synucleine. In industrialized countries, PD occur for about 0,6 à 0,8 % patients aged between 65 to 69 years and 2.6 to 3.5% over 89 years. In the most advanced forms in addition to the most usual symptoms, PD is complicated by confusion. As drugs may be at the origin of hallucinations, they are distinct from effects which might differs from non-

secondary side-effects of the drugs. The physical signs are not identical on the right and left side of the patient. Tremors are presents for 2/3 of patients. They are seen during the rest, most generally on hands, sometimes on chicks and legs. The non-genetic causes of PD are the following.

- Speech changes: the patient speaks more rapidly and with a more feeble voice
- Writing troubles: (micrography)
- Swallowing difficulties, including the own saliva of the patient
- Equilibrium perturbations: a tendency to fall during displacements

Sleep troubles are frequent as well as urinary incontinence. Constipation is also repeated. Lévodopa (or L-dopa) is transformed in dopamine in the brain. All the drugs possess components that inhibits their degradation by organism. The risk of developing PD is increased 20-30 fold if the mutation is present.

COMT metabolizes levodopa into 3-O-methyldopa. Dopamine agonists are less effective than levodopa at controlling PD motor symptoms. Dyskinesia due to dopamine agonists are rare in younger people, but along with other complications, become more common with older age. Therefore, dopamine agonists are usual in the initial stages and possibly to control in those in advanced states.

MAO-B inhibitors increase the amount of dopamine. They have been found to help alleviate motor symptoms when used as monotherapy. Selegiline delays the need for levodopa commencement.

Devices and Drugs Used for the Treatment of PD

1. Placement of an electrode into the brain: The head is stabilized in a frame for stereotactic surgery. Deep brain stimulation (DBS) involves the implantation of a medical device called a neurostimulator. Generally, DBS is associated with 30–60% improvement in motor score
2. Exercise programs are recommended in people with PD, improving motor symptoms, mental and emotional functions and quality of life. Occupational therapy (OT) aims to promote health and quality of life
3. Palliative-care team members help patients to make the best decision. Muscles and nerves that control the digestive process may be affected by PD, resulting in constipation minimizing the consequences of gastrointestinal dysfunction
4. Medication has improved the prognosis of motor symptoms. In people taking levodopa, the progression time of symptoms to a stage of high dependency may be over 15 years. As the disease advances, disability is more related to motor symptoms that do not respond

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adequately to medication, which appear in up to 50% of individuals after 5 years of levodopa usage. All of these symptoms greatly increase disability. Cognitive decline and dementia, old age at onset, a more advanced disease state and presence of swallowing problems are all mortality risk factors

5. Expecting that the neural cells will be incorporated and largely replaced into the brain by induced pluripotent stem cell derived dopaminergic neurons. Gut microbiota produces lipopolysaccharide interfering with the normal function of α -synuclein

Conclusion

Parkinson's Disease (PD) is characterized by tremor, stiffness, rigid muscles, bradykinesia, slowness of movement, instability leading to falls, declined memory, cognitive and talking difficulties, fatigue, writing modifications (micrography) and dementia. In addition, depression, urinary (bladder) problems, constipation, decreased ability to smell and sleep disruption are among the symptoms associated to the PD. Mortality ratios are twice those of unaffected people. Death is occurring 7 to 15 years after the beginning of the PD.

Conflict of Interest

The authors declare no conflict of interest.

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