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Introductory Chapter - Genetic and Biochemical Factors in Parkinson's Disease

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1. Introduction

Worldwide increased life expectancy, which was seen in the second half of the twentieth century, has contributed to an increased number of cases of diseases typical of old age, including Parkinson's disease (PD). At present, PD is one of the most common degenerative diseases of the central nervous system (CNS) and affects nearly 2% of the population over the age of 65 and 5% over the age of 85. Moreover, the estimates show that in the face of population aging, the number of patients with this neurodegenerative disease will maintain an upward trend.

Although PD was first described nearly 200 years ago, it is still an incurable disease and its cause is not fully understood. It is known that disturbances in the structure of two pathological proteins of PD, alpha-synuclein (ASN) and Parkin, may lead to the formation of Lewy bodies (LB), which lead to damage of dopaminergic neurons and decreased levels of dopamine (DA). The disturbances in the structure of ASN and Parkin are due to both genetic and environmental factors. Despite numerous reports in the literature concerning the molecular basis of this disease, little is known about the interactions occurring between the individual genes responsible for encoding these proteins and the pathological manifestation of PD [1–8].

As a result of the lack of knowledge of PD pathomechanism, it is also not possible to have early, potentially intravital, diagnosis of this disease. Currently, the diagnosis of PD is based on clinical criteria, supported with neuroimaging, and is only a probable diagnosis of this disease. Reliable detection of PD is only possible after testing for the presence of neuropathological changes in the brain that is typical for this disease and is carried out *postmortem*. It is known that lack of early and definite diagnosis of PD may make it difficult to provide effective therapy to slow down the progression of the disease and can decrease the quality of life of patients [9].

PD belongs to the disorders of the extrapyramidal system (EPS), in which we observe symptoms in a number of nonmotor (NMS) symptoms, such as dementia, hallucinations, depression, and orthostatic hypotension, in addition to motor disorders [9–12].

Many studies are currently being conducted on the pathogenesis of PD in many research centers around the world, and knowledge of this disease is growing rapidly. In the last two decades, new genes associated with PD (PARK1-PARK18) were discovered, and there was a remarkable progress of surgical treatment techniques using deep brain stimulation (DBS) of selected brain structures [6].

2. Genes important for pathogenesis of Parkinson's disease

The causes of PD are both genetic and environmental. To date, a number of genes associated with the presence of PD have been described within distinct patient families (familial PD, FPD) and/or corresponding locations of genes identified as PARK (PARK1-PARK16) as described in [5]. It is believed that genetic factors include mutations of the *SNCA* gene (PARK1, PARK4), encoding the ASN protein, may also be responsible for increased susceptibility in sporadic PD (SPD) [6,7].

It has been shown that approximately 5–10% of all known PD patients are people with FPD, a monogenic condition that is classically inherited in a recessive or dominant manner. The molecular mechanisms responsible for RPD also play an important role in the pathogenesis of SPD.

Moreover, SPD occurs due to the influence of various factors, including signal transduction, vesicular transport, the process of autophagy, and mitochondrial dysfunction. It is also suggested that the clinical heterogeneity of PD, including SPD, may involve interactions not only in genetic and environmental factors, as well as in the reactions between genes, such as *SNCA*, *PRKN*, *LRRK2*, *PINK1*, and their protein products: ASN, Parkin, LRRK2, and PINK1, respectively [1–8].

3. Oxidative damage and hyperhomocysteinemia and biogenic amines in Parkinson's disease

It is known that the degenerative process in PD occurs for many years before the manifestation of clinical symptoms. There are several hypotheses to explain the pathological processes in PD. One of them indicates the participation of oxidative stress in the damage that occurs to dopaminergic neurons [13–15]. In oxidative neuron damage, it is possible that impaired metabolism of homocysteine (Hcy) and other biothiols, such as methionine (Met), cysteine (Cys), and glutathione (GSH), may be involved. Moreover, Hcy, or its oxidative product homocysteine acid, may increase prooxidative activity, most probably through its direct interaction with NMDA receptors (as agonist of NMDA receptor). Many of the literature reports indicate that pathogenesis of PD is associated with increased apoptosis [13,15–18].

Homocysteine in physiological condition is converted to Met and Cys, depending on the activity of enzymes MTHFR, MTR, MTHFD1, and CBS, encoded by genes *MTHFR*, *MTR*, *MTHFD1*, and *CBS*, respectively [13]. Activity of these enzymes depends on the genotype of the gene encoding a given enzyme. As also shown in [13], the following genotypes are included in the pathogenesis of PD, for Hcy metabolites, Met [MTR, AA (A2756G)], Cys [MTR, AG (A2756G)], and Met/Hcy [MTHFR: CC, CT (C677T), and AA (A1298C), and GG (G1793A); MTHFD1 AA (G1958A); MTR AA (A2756G)] and Hcy [MTHFR: CT (C677T) and GG (G1793A); MTR, AG (A2756G)].

Biogenic amines are also involved in the generation of oxidative stress in the course of PD and include catecholamines such as norepinephrine (NE), epinephrine (E), DA and serotonin (5-HT). Catecholamines are subject to nonenzymatic autoxidation and form highly reactive derivatives. Increased endogenous neurotoxin levels may lead to the formation of ubiquitin and ASN-positive cytoplasmic inclusions (LB) [10–12]. Regulation of plasma biogenic amine levels in PD affects both coding by genes the enzymes responsible for metabolism (*COMT*, *MAO-A* and *MAO-B*), and the amines' transport and reuptake (*NET*, *DAT*, *SERT*). Polymorphisms in genes related to trading of biogenic amines may influence the manifestation of this disease, especially *NET* GA (c.1287G>A) and *NET* AA (c.1287G>A) [12].

4. L-Dopa therapy effects in Parkinson's disease

The strategy of therapy of patients with movement disorders, particularly PD, is based essentially on the strengthening of dopaminergic transmission with exogenous L-dihydroxyphenylalanine (L-dopa) and DA agonists [9]. It has been shown that long-term treatment of PD patients with L-dopa improves their motor functions by increasing the level of central DA.

At the same time, it has been shown that increasing dopaminergic neuronal damage in PD may reduce the effectiveness of L-dopa and DA agonist therapy. Moreover, in patients with PD, due to the loss of dopaminergic neurons in the *striatum*, L-dopa may penetrate other dopaminergic neurons, especially the mesolimbic, and lead to emotional and neuropsychiatric disorders in these patients.

L-Dopa therapy in PD may also induce cardiovascular disease and stroke by increasing the plasma levels of risk factors for vascular diseases, such as asymmetric dimethylarginine (ADMA) and Hcy. Moreover, L-dopa leads to increased levels of 8-oxo-2'-deoxyguanosine (8-oxo2dG), a parameter of oxidative stress, and changes levels of biogenic amines and proteins involved in apoptosis [9,15,19–21].

5. Summary

Although PD has been known and studied since the early nineteenth century, the cause of death of dopaminergic neurons remains unknown and the treatment of this disease focuses on treating symptoms.

In PD, as in other neurodegenerative diseases, research seeks to determine biomarkers to enable early definite diagnosis of this disease and the development of effective neuroprotective or modulatory disease drugs. PD patients who do not respond to conventional drug treatment are currently treated using one of the new surgical techniques, including DBS.

Currently, research in PD is looking for a therapy that can ensure effective antiparkinsonian treatment, eliminate dyskinesia, and slow or stop the progression of this disease.

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