Chapter 2

Dopamine and Early Onset Parkinson's Disease

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Abstract

Parkinson's disease (PD) is divided into early-onset (EOPD) occurring at the age of fewer than 45 years of age and late-onset PD (LOPD) above 45 years of age. EOPD accounts for 5–10% of all the cases with PD. It is thought that occurrence in this age is connected with genetic factors, mutations in e.g. *PRKN, PINK1, DJ-1* and changes in proteins it is encoded. The loss of dopaminergic neurons in the nigrostriatal system leads to decreased dopamine (DA) concentrations. Pathogenic PD proteins may affect the DA level. The lower level of DA may be responsible for movement-related symptoms. EOPDs have a slower progression of the disease and a longer disorder duration but tend to develop dyskinesias and motor fluctuations earlier than LOPD. Currently, the diagnosis of PD is based on clinical criteria, supported neuroimaging like MRI or PET. Understanding the pathogenesis of the EOPD may be contributing to improving diagnostics and effectiveness of pharmacotherapy.

Keywords: molecular factors, dopamine, Parkinson's disease of early onset

1. Introduction

Parkinson's disease (PD) is one of the most common and spontaneous degenerative disease of the central nervous system (CNS) that is characterized by classical motor symptoms like bradykinesia, muscular rigidity, rest tremor, or postural instability [1]. It is estimated that approximately 5 million people worldwide suffer from PD. The frequency of disease increases with age; there are 1% of people older than 60 years and 5% of people over 85 years [2–4]. It seems that males suffer more often than females [5]. Furthermore, the estimates indicate that the number of PD patients will maintain increase trend because of population aging.

PD usually develops in the fifth or the sixth decade of life and is called late-onset PD (LOPD), but in a small group of patients, it is diagnosed even before the age of 40 years. The definition of early-onset PD (EOPD) is arbitrary. Some authors defined this disorder with an age of onset (AOO) below 40 years, others even below 50 years, but usually, it refers to age less than 45 [6, 7]. According to the literature data, 5–10% patients suffer from EOPD. EOPD can also be subdivided into the group called juvenile PD with AOO less than 21 years [8].

The main factor in PD pathology is loss or degeneration of dopaminergic neurons in the substantia nigra (SN). Although this disease was described more than 200 years ago, its cause is still not fully understood. It is considered that the pathogenesis depends on both genetic and environmental factors, but genetic changes are main causes in about 5–10% of the PD patients [9]. Some genes and its proteins associated with EOPD like *PRKN* gene and the Parkin protein or *PINK1* gene are identified.

The phenotype of PD is various and related to AOO. It includes classical motor symptoms and non-motor symptoms such as disorder of mood, cognitive, behavioral, sensory, and autonomic dysfunctions (e.g., orthostatic hypotension and urogenital dysfunction) [10]. Patients' characteristic of EOPD and LOPD is summarized in **Table 1**.The study of Wickremaratchi et al. [7] showed that features like tremor, rigidity, response to most common treatment, or presence of dystonia and dyskinesia's have linear changes (increasing or decreasing). However, dystonia demonstrates the highest risk of occurrence among EOPD and reduction among LOPD patients.

The proper diagnosis of PD is very important. Nowadays, there are a lot of neuroimaging methods that can be used to increase the accuracy of differential diagnosis, but none of them have been endorsed to routine use in clinical practice [11, 12].

Features	EOPD	LOPD
Mean age of onset (years)	44	72
Survival from onset (years)	27	10
Mean age at death (years)	71	82
Tremor at onset, only (%)	45	59
Bradykinesia and tremor at onset (%)	23	9
Bradykinesia at onset, only (%)	32	25
Postural instability at onset (%)	0	7

Table 1. Patients' characteristic of EOPD and LOPD [8].

2. Dopamine and pathogenesis of Parkinson's disease

Dopamine (DA) is the organic chemical of the catecholamine family and precursor for noradrenaline. It is synthesized in presynaptic neuron from tyrosine to L-dihydroxyphenylalanine (L-dopa) via tyrosine hydroxylase. Subsequently, aromatic amino acid decarboxylase removes a

carboxyl group, form neurotransmitter, which is packed into synaptic vesicles. DA is released into the synapse during stimulation, actives dopaminergic receptors, and evokes a response in the postsynaptic cell [13]. It plays a pivotal role in the generation of normal movements by transmission information from SN to the striatum, where movements are initiated and controlled facility and balance [14].

The pathomechanism of PD is progressive and subsequent degeneration of neurons in SN, which results in the decreased level of DA in the dopaminergic neurons. Further, there is also the presence of Lewy bodies (LBs), intracytoplasmic eosinophilic inclusion bodies, in others neurons in SN. The literature indicates that loss of 60–70% of dopamine neurons in SN is presented as PD motor symptoms [15]. Pathogenesis of PD involves both environmental and genetic factors. It is thought that the pathways involved in PD are impairment of cellular clearance pathways, protein aggregation, oxidative stress, mitochondria dysfunction, and neuroinflammation (**Figure 1**) [16–18].

α-Synuclein (ASN) is a major component of LB [19]. Aggregation of ASN is considered to be engaged in the pathogenesis of PD in consequence of the cellular clearance pathway like

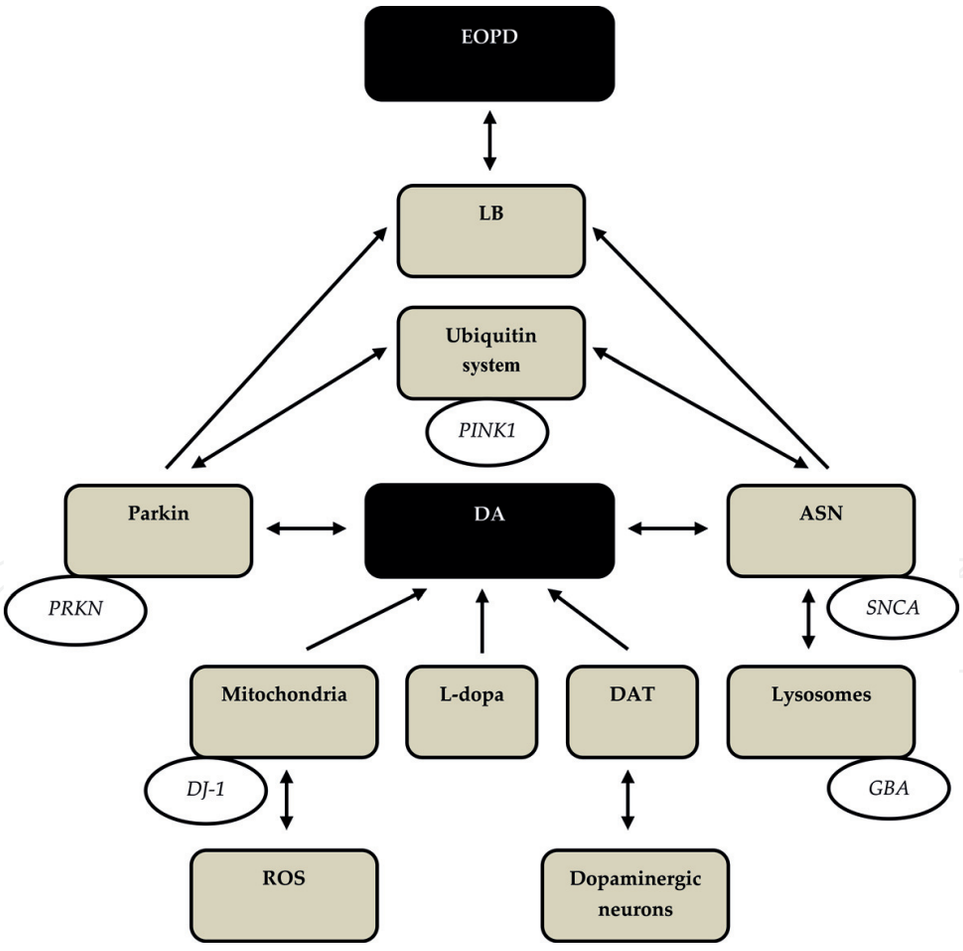

Figure 1. Association between DA in Parkinson's disease, EOPD and genetic and biochemical factors. EOPD—early-onset Parkinson's disease, LB—Lewy bodies, DA—dopamine, ASN—α-synuclein, L-dopa—L-dihydroxyphenylalanine, DAT—dopamine transporter, ROS—reactive oxygen species.

ubiquitin-proteasome and autophagy-lysosome [20]. The literature indicates that ASN modulates dopamine transporter (DAT) activity. DAT is responsible for removing DA from the synaptic cleft. It is showed that the polymorphisms in gene coding DAT (*DAT1)* are engaged in the detoxication mechanism and oxidative stress [21]. Membrane depolarization of DAT enhances plasma membrane ASN localization, which subsequently increases DA efflux [22]. The study of Mazzulli et al. [23] shows that the loss of lysosomal enzyme glucocerebrosidase (GBA) causes interference in protein degradation and accumulation of ASN, and GBA substrate is associated with the amyloid formation of purified ASN. On the other hand, GBA activity in neurons of PD brain is inhibited by ASN.

Oxidative stress is a disturbance in the balance between prooxidant and antioxidant homeostasis and production of reactive oxygen species (ROS) [24]. The main mitochondrial site of generation ROS is complex I [25]. There is a direct relationship between mitochondrial dysfunction and decreased activity of complex I among PD patients [26]. Moreover, it is known involvement of such genes like *PRKN, PINK1,* and *DJ1* in mitochondrial PD pathogenesis [18]. One of the causes of the increase of oxidative stress and ROS in dopaminergic neurons is self-oxidation of DA to quinones (DAQs).

DAQs are electrophilic species, very reactive toward cellular nucleophiles, which effect damage of cells. DAQs can bind to Parkin and promote its aggregation. Thus, this protein losses its function. It seems that DAQs are more responsible for inactivation of Parkin than ROS [14]. The study of Bisaglia et al. [27] shows that DAQs interact with ASN by inhibition of ASN fibrilization and stabilizing ASN/DAQ oligomers. It seems that DAQs can also modify the structure of DJ-1 through modifications in cysteine residues of its protein [28].

Kitada et al. [29] show that mutations in *PINK1* gene, which is associated with EOPD, and inactivation of encoded protein impair DA release. However, they do not alter the levels of DA, a number of dopaminergic neurons, DA synthesis, and levels of DA receptors. These results indicate that this impairment is sufficient to cause dysfunction of the nigrostriatal circuit by deficits in synaptic plasticity.

3. Genetic risk factors for early-onset Parkinson's disease

The etiology of EOPD is not completely explained. It seems that genetic factors, environmental factors, or both of them may play an important role in the pathogenesis of this disease. There have been identified several genes and their mutations associated with EOPD, but new loci are still being identified. Most of these genes are inherited autosomal recessive, for example, *PRKN, PINK1, or DJ1,* but some of them are associated with the autosomal dominant pattern, for example, *SNCA* [30].

3.1. *PRKN* gene

One of the most important genes involved in the pathogenesis of EOPD is *PRKN* (PARK2) that encodes 465 amino acid-long Parkin protein. Parkin is a part of multiprotein E3 ubiquitin

ligase complex and is involved in the regulation of mitochondrial quality control pathway and promotion selective autophagy of depolarized mitochondria (mitophagy) [31]. Moreover, overexpression of this protein leads to elevated expression of complex I subunits and decreased the accumulation of ROS [32]. Parkin interacts with other proteins such as PINK1, which promotes the mitochondrial translocation of Parkin [33]. There is also a suggestion about a role in DA utilization in human dopaminergic neurons by controlling the precision of dopaminergic neurotransmission and DA oxidation [34].

PRKN gene is located on chromosome 6q26 and consists of 12 exons. There are various data results about the frequency of mutations in *PRKN* that implies a possible role of the environment [35]. Some of them indicate that they are responsible for 9% of cases of EOPD, but others suggest even twice higher number—18% among patients with age of onset (AOO) before 45 years and 77% of those with AOO before 20 years. Mutations in *PRKN* gene are also more frequent in patients with a positive history than in sporadic cases [36, 37]. Pathogenic mutations in *PRKN* gene cause losing quality control pathway and accumulation of damaged mitochondria, what in consequence leads to elevation of ROS, cell death, and PD [31]. There have been identified more than 100 mutations in *PRKN* gene, which includes deletions, insertions point mutations, and large arrangements [38]. Some of them seem to be pathogenic like Q171X, R275W, G284R, or T425 N, but another likely to be non-pathogenic, for example, A82Q, L174 L, or L261 L [35, 39]. Hedrich et al. [40] indicate that R275W mutation is the most common point mutation in EOPD and is always combined with other changes in *PRKN* gene.

3.2. *PINK1* gene

Another gene which mutations are involved in the occurrence of EOPD is phosphate and tensin homolog (PTEN)-induced putative kinase 1 (*PINK1).* It is a 581 amino acid ubiquitously protein kinase, which includes a 34 amino acid mitochondrial targeting motif and a highly conserved protein domain (amino acids 156–509, exons 2–8) showing a high degree of homology to the serine/threonine kinases [38, 41]. It is widely expressed in human brain and plays a role in the mitochondrial response to oxidative stress, degradation of impaired mitochondria by activation this organelle's autophagy (mitophagy) by Parkin, and regulation of Parkin localization [42, 43]. Morais et al. [44] also show that modifications in *PINK1* may cause elevated ROS production and impaired DA release.

Mutations in *PINK1* (PARK6) gene are the second most common cause of AR EOPD [38]. *PINK1* is mapped to chromosome 1p36.12 and contains eight exons. There have been reported more than 100 *PINK1* gene mutations including large deletions, frame shift mutations, nonsense, or missense mutations, which cause loss of protein function [45]. It is considered that mutations in this gene are responsible for 14% of EOPD cases, but there is wide variation between different ethnic group [37, 46]. The study of Kilarski et al. [36] indicates that majority of mutations are homozygous and they are more common in Asian populations than in white patients or Latin American. One of the reported mutations in *PINK1* was Q456X in exon 7 by Bonifati et al. [46]. It is a nonsense mutation that results in a premature stop codon. The study of Siuda et al. [43] suggests that this mutation leads to complete loss of PINK1 at the RNA level in skin fibroblast derived from a patient, what causes dysfunction of Parkin. Other mutations

in this gene associated with EOPD and are likely to be pathogenic Y258X, R276X, M318 L, and A427E [39, 47, 48]. The literature data also indicate occurrence of such mutations that seems to be non-pathogenic or the significance is unknown in EOPD patients like R312R, A339T, D391D, G411S, T420 T, D525N, and S576S [39].

3.3. *DJ-1* gene

The third gene associated with EOPD is *DJ-1* (PARK7). It encodes a 189 amino acid-long protein, which is a mitochondrial peroxidase. DJ-1 protein has homodimeric structure, which is ubiquitously expressed in brain areas and also in peripheral tissues [49, 50]. The literature indicates multiple functions of this protein-like protection cells against oxidative stress, acting as a chaperone and protease or interactions with other known PD-proteins such as Parkin or PINK1 [51–53]. Moreover, it plays an important role in the maintenance of mitochondrial complex I activity and defense function against cytotoxicity induced by toxic ion metals like copper or mercury [53, 54]. DJ-1 protects against dopamine toxicity and control the vesicular sequestration of DA [55]. Mutations cause instability of a dimeric structure, which is physiological form, and lack of expression [45]. Modified proteins are not properly folded, unstable, and degraded by the proteasome what results in a reduction of neuroprotective function and antioxidative activity [38].

The *DJ-1* gene is located on chromosome 1p36.23 and contains eight exons, where first two of them are noncoding and alternatively spliced in mRNA [56]. The *DJ-1* gene mutations in EOPD are rarer than *PRKN* and *PINK1* mutations with overall frequency 0.4%, which increases with familial cases to 0.8% [36]. The *DJ-1* locus was identified in a Dutch family with AR EOPD [57] and that led to the identification of mutations in *DJ-1* gene of two families [56]. They have been identified in nucleotide substitutions like missense, truncating, spic-site mutations and also large deletions [58]. The study of Abou-Sleiman et al. [59] identified two mutations in *DJ-1*. The first one was homozygous M26I in an Ashkenazi Jewish patient, which causes substitution of methionine for isoleucine. The second was a substitution at codon 149 in which highly conserved polar aspartate residue exchanges to non-polar alanine (D149A). There have been found another mutation in EOPD like A104T [60] or L10P in Asian populations. The study of Guo et al. [61] also suggests that two identified mutations in the Italian population, D24A and F162 L, may cause PD in the case of presence in homozygous or compound heterozygous state with other mutations. The literature data indicate that there was a considerable reduction of DAT binding in the Turkish patient with an E64D mutation in the homozygous state. These results show a significant decline of presynaptic dopaminergic afferents [62]. Moreover, the clinically unaffected sister of EOPD patient (homozygous for E64D) had demonstrated reduction of DA uptake in comparison with a clinically unaffected brother, who has the heterozygous state for this mutation.

3.4. *GBA* gene

The *GBA* gene is mapped to chromosome 1q22 and encodes the lysosomal enzyme GBA. It is β-glucosidase that catalyzes the breakdown of glucose and ceramide, which are a precursor for glycosphingolipids and sphingomyelin occurring in nervous tissues [63, 64]. Mutations in *GBA*

gene play an important role in neurological disorder like PD. They account for 5% of all PD cases, but the frequency of occurrence is ranged from 10.7 to 31.3% of Ashkenazi Jewish patients with PD and from 2.3 to 9.4% in patients of other populations [65]. The most common mutation in the Ashkenazi Jewish is N370S, but in Caucasian populations are N370S and L444P. There have been also identified such mutations in EOPD as H255Q, E326K, D409H, or R329H [66]. The activity of this protein is decreased in heterozygous mutations in PD patients in comparison to non-mutated carriers [67]. It is suggested that they cause dysfunction of the autophagy-lysosome pathway, mainly impairment in macroautophagy and chaperone-mediated autophagy involved in accumulation, aggregation, and transmission of ASN [64].

Moreover, homozygous mutations in *GBA* gene leads to Gaucher's disease (GD), the most common lysosomal storage disorder due to deficiency of enzyme GBA [68]. The literature indicates that mutations of *GBA,* even in the heterozygous state, may be associated with this disorder [69]. Patients with GD have an increased risk of PD and parkinsonism features. It seems that there is no GD genetic variant linked with PD, but N370S is the most frequent mutation detected in American, European, and Ashkenazi Jewish population [65, 68].

3.5. *SNCA* gene

SNCA (PARK1 and PARK4) gene was the first gene ever identified as causal PD. It is an inherited autosomal dominant pattern and located to chromosome 4q22.1 [30]. *SNCA* gene encodes ASN, but the functions of its are still not completely understood. It is known that it is the main component of LB [19]. ASN reduces protein kinase C (PKC) activity, which is sensitive to oxidative stress and protects dopaminergic cells against apoptosis [70]. It can also regulate glucose levels by increasing tissue glucose uptake, modulate calmodulin activity, and act as a molecular chaperone and antioxidant by protecting dopaminergic neurons against oxidative stress [71–74]. Moreover, ASN can decrease the activity of tyrosine hydroxylase and thus regulates the production of DA and control its levels [75]. It also interacts with other proteins including Parkin or DAT by decreasing its activity [76].

One of the most common mutations in *SCNA* gene associated with EOPD is A53T. It was firstly identified in members of Contursi kindred and three families from Greece, but later A53T was also found, for example, in Sweden and Korean population [77–79]. They were also described in such mutations as A30P and E46K related to EOPD [37, 80].

4. The phenotype of early-onset Parkinson's disease

Patients with EOPD are characterized as younger AOO and longer disease duration than patients with LOPD [81]. Some symptoms vary among patients (**Table 2**), but classical motor symptoms are mainly affected.

EOPD with *PRKN* mutations is characterized by excellent response to L-dopa treatment and in consequence presence of dose-related fluctuations or dyskinesias after around 7 years of pharmacotherapy. The most common motor features are limb tremor and bradykinesia, but

Gene (locus)	Location	Selected mutations in EOPD patients	Inheritance	Clinical phenotype
PRKN (PARK2)	6q26	Q171X, R275W, G284R, T425N, A82Q, L174L, L261L	Recessive	Tremor, bradykinesia, urinary dysfunctions
PINK1 (PARK6)	1p36.12	Q456X, Y258X, R276X, M318L, A427E, R312R, A339T, D391D, G411S, T420T, D525N, S576S	Recessive	Foot dystonia, gait impairment, excellent L-dopa responsiveness
DJ-1 (PARK7)	1p36.23	D149A, A104T, L10P, D24A, F162 L, E64D	Recessive	Similar to *PRKN*
GBA	1q22	N370S, L444P, H255Q, E326K, D409H, R329H	Recessive	Mild Gaucher's symptoms, cognitive impairment
SNCA (PARK1, PARK4)	4q22.1	A53T, A30P, E46K	Dominant	Rigidity, rapid progression

Table 2. Genes implicated in EOPD and its clinical phenotype [30, 39].

there are also reported such as poor balance or freezing episodes. Patients with *PRKN* mutations have autonomic symptoms like urinary urgency (45%), impotence (28%), and orthostatic faintness (13%) [82]. They also have a lower frequency of excessive daytime sleepiness than general PD population, and insomnia is considered as a most common sleep problem [83]. The results of Mini-Mental State Examination score (MMSE) in *PRKN* patients are ranged 30–25; thus, cognitive functions are normal [82]. The study of Kim et al. [83] showed that the patients with two mutations have significantly younger AOO and longer duration of the disease in comparison to patients without *PRKN* mutations. Moreover, they can have a positive family history with PD and use a lower dose of L-dopa. Patients can also present psychiatric dysfunction like depression, psychosis, obsessive–compulsive disorder, or anxiety [84]. Some literature data indicate that *PRKN* mutation carriers and non-mutation carriers are clinically indistinguishable [85].

Most of EOPD patients with mutations in *PINK1* gene show typical symptoms of the disease resting tremor, rigidity, and bradykinesia. They have very good and sustained response to L-dopa treatment [46]. The Ibáñez et al. [86] study showed that even after 45 years of disease duration, the patient has a good response to L-dopa therapy. Moreover, there is a very slow progression of the disease and patients have no worsening for several decades. Siuda et al. [43] demonstrated two homozygous Q456X mutation carriers in a Polish family, who developed their first symptom, foot dystonia, in 16 and 27 years. Subsequently, patients suffered from progressive gait difficulties and had sensory symptoms in the lower limbs. It seems that disease onset in the lower limbs and early gait impairment can be characteristic for PD with *PINK1* mutations [86, 87]. Besides having classical motor symptoms, patients with *PINK1* mutations present L-dopa–responsiveness dystonia or restless leg syndrome (RLS) [81]. Cognitive impairment is rare and appears only in cases with a long duration of PD [86].

The phenotype of *DJ1*-related EOPD varies among mutations. Patients with the M26I mutation are characterized similar phenotype as *PRKN* mutation carriers. They have early leg dystonia before starting treatment and psychological disturbance, mainly anxiety [59]. The study of Hering et al. [62] showed that EOPD starts with slowing of movements and stiffness in the left

leg and arm among patient with identified novel E64D mutation. Moreover, the first features were sleep disturbances, depression, and speech difficulties. In the patient with bradykinesia, rigidity and postural tremor occurred only on the left side of the body, but there was no problem with cognition. The observation of Abbas et al. [88] indicate that the patient with missense mutation I105F found in exon 5 presented asymmetric onset, moderate L-dopa response, but no pyramidal features or dystonia. It seems that special feature in this patient was extreme motor restlessness to L-dopa. However, in the same study, it is demonstrated that homozygous R98Q variant is responsible for good L-dopa response and the treatment induces dyskinesia.

GBA mutation carriers have significantly younger AOO in comparison to non-carriers [89, 90]. Patients characterize of good or excellent response to L-dopa therapy and present a typical PD phenotype. Furthermore, some of them present impressive to subthalamic nucleus deep-brain stimulation. There are also cases of *GBA* patients that affect depression [90]. The study of Sato et al. [89] indicates that *GBA* mutation carriers have a positive history of PD in families. They present poorer motor progression, more often postural instability, persistent asymmetry, and responsive for L-dopa for more than 5 years [91]. According to the literature data, *GBA* mutations are associated with cognitive impairment, which is revealed by a lower MMSE score [92]. It is considered that patients with both GD and PD present mild Gaucher's symptoms [65].

The phenotype of *SNCA*-related EOPD consists of typical features for this type of the disease—asymmetric onset, good responsiveness for L-dopa in initial time, and early motor complications. The literature indicates that *SNCA* A53T mutation carriers with long-term PD present cognitive defects like dementia and average or inconsiderable in shorter term one. Besides, it was noted psychiatric syndromes, for example, depression, anxiety, dysautonomia, or olfaction impairments [93]. There can be observed numbness in the first of the disease, insomnia and occasional hypotensive attacks [94]. Whereas G51D carrier has phenotype differing from those with A53T. Patient characterizes the rapid progression of the disease, which consequently leads to loss of autonomy and death in few years. There were also noted manifested cognitive deterioration, visual hallucinations, and seizures [95]. The study of Somme et al. [96] shows that E46T mutation in early stages is also associated with a visual hallucination, sleep disorder, rigidity, and dementia.

5. Neuroimaging of early-onset Parkinson's disease

A lot of neuroimaging techniques are used to diagnose PD properly, follow the progress, and also get to know the neurobiology mechanism involved in revealing the disease. The most commonly used methods are magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and transcranial sonography (TCS). There are also multimodal neuroimaging techniques that combine imaging with complementary modalities to increase the benefits of examination.

PET imaging is a technique using radiolabeled agents like ^{11}C, ^{18}F, and ^{15}O. It is more sensitive and presents a better special resolution in comparison to SPECT, which employs radioisotopes ^{123}I or ^{99m}Tc. It is thought that SPECT is cheaper, more widely available, and a valuable imaging modality for many PD applications [97]. It seems that Technetium^{99m}-labeled tropane derivative (^{99m}Tc-TRODAT-1) can be used to reveal dysfunction of dopaminergic system by binding DAT [98]. It was also showed that striatal DAT-binding potential was 34% lower among EOPD than LOPD patients [99]. The study of Shyu et al. [100] identified lower uptake of ^{99m}Tc-TRODAT-1 in the putamen, but normal in the caudal nucleus among patients with *PRKN* mutations in early stages of EOPD. There is more symmetrical loss demonstrated in both structures in the latter stages of the disease. However, the PET results of Nagasawa et al. [101] show that the function of presynaptic dopamine terminals does not correlate with PD severity and degrees of main symptoms.

MRS is a kind of magnetic resonance for identifying many endogenous compounds involved in the pathomechanism of PD like DA, γ-aminobutyric acid (GABA), and glutamate, so it gives an opportunity for probing biochemical systems [102, 103]. It allows research neurochemicals directly, without invasion and radiation exposure.

There is also another kind of resonance MRI in patients with EOPD. MRI creates images of the human body by detecting spin properties of nuclei [97]. MRI is not able to directly image dopaminergic neuronal loss, but it can provide complementary data to those obtained with nuclear tracer imaging [104]. The study of Wang et al. [105] shows that pathological asymmetry between both hemispheres in NG pathways in the early stage of EOPS using an MRI method.

TCS is another technique used in PD. It is a noninvasive, validated ultrasound method for demonstrating characteristic alterations of deep brain regions especially SN, but also lenticular nucleus (NL) or ventricles [106]. It is less expensive than the previously described tools, that is why it can be an important advantage of its application [97]. The literature indicates that TCS-MRI fusion allows analyzing SN and NL echogenicity as highly sensitive and specific markers for EOPD [107].

There are also multimodal imaging for imaging structure and metabolism like PET/CT. Using this method, the study of Shi et al. [108] shows the unequal radioactive distribution of ^{18}F-2-deoxy-D-glucose among patients with compound mutations in the *PRKN* gene. Moreover, the authors observed the reduction of ^{11}C-2 β-carbomethoxy-3 β-(4-fluorophenyl) tropane uptake in the caudal putamen.

6. Summary

The occurrence of EOPD is associated with molecular factors both genetic and biochemical ones. The presence of various genetic variants such as *PRKN* gene is associated with Parkin protein, the *PINK1* gene affecting the efficiency of the ubiquitin-proteasome system, the *DJ-1* gene linked with mitochondria, *GBA* gene connected with lysosomes and *SNCA* gene encoding ASN may accelerate revealing of PD. It seems that discovering the relationship

between genetic bases and protein parameters may lead to explain the causes of appearance PD depended of age. Furthermore, in the future, it could entail with bases for earlier diagnosis of EOPD and in consequence introduction of more effective pharmacotherapy.

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